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FLOYD ELWOOD KEENE
1881—1938

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IN MEMORIAM

FLOYD ELWOOD KEENE
1881-1938

FLOYD ELWOOD KEENE, member of the Advisory Editorial Board, was born Oct. 9, 1881, in Kewanee, Illinois. His youth was spent in Peoria, Illinois, where he received his preliminary education. Having graduated from the High School there, he entered the University of Pennsylvania Medical School and graduated in 1904. From his early medical school days he showed a keen interest and appreciation of medical sciences and applied himself to these most diligently throughout his academic career. His acute mind soon established him as one of the outstanding and scholastically brilliant members of his class.

Upon completion of his undergraduate career, and because of his unusual ability, he was selected as an interne for the University Hospital, which interneship he completed in 1906. By this time he had made many friends and admirers among his instructors, chiefs, the older men of the faculty, and the profession, who urged him to undertake postgraduate study, which advanced instruction he obtained in Berlin and Vienna, during 1907 and 1908.

His immediate association with the then eminent Goodell Professor of Gynecology, Dr. John G. Clark, upon his return, started his rapid rise in this specialty. Dr. Keene for many years was Dr. Clark's first assistant as well as his personal and much admired friend. He held the Chair of Assistant Professor of Gynecology at the University of Pennsylvania from 1922 until 1927. During his assistant professorship he soon became, under Dr. Clark's able supervision, a skillful operator and brilliant author. He assumed a deep interest in the study and early recognition of cancer and its treatment and in a large measure was responsible for the remarkable end-results obtained in this clinic. He soon became an authority on the use of radium in the treatment of both benign and malignant uterine lesions. As the technique of treatment changed from time to time, he was instrumental in bringing about what today is the well-recognized method of dealing with malignancy.

At Dr. Clark's untimely death, Dr. Keene succeeded him as Goodell Professor of Gynecology, in 1927, which Chair he held until his death.

During his medical life in Philadelphia, he made many sincere friends throughout the country, among the older as well as the younger members of the profession. He endeared himself to his patients by his kindness and sympathy, often sacrificing his own personal health to minister to the sufferings of others.

Dr. Keene was a member of the American Medical Association; American College of Surgeons; American Gynecological Society; Surgical Research Society; College of Physicians of Philadelphia; Obstetrical Society of Philadelphia; Philadelphia Academy of Surgery; Philadelphia Pathological Society, and Phi Delta Theta, Alpha Omega Alpha (Hon.), and Phi Alpha Sigma (Medical) Fraternities. In some of the many societies of which he was a member, he held high rank, being Secretary for five years and subsequently President of the American Gynecological Society from 1933 to 1934; President of the Philadelphia Obstetrical Society from 1931 to 1932.

Dr. Keene published many noteworthy articles relative to his specialty. An alert observer, quick to accept sound advances, he became one of the foremost gynecologists of his day.

He served overseas with distinction, as a member of Base Hospital No. 20 U.S.A. He married Marthe Bussiere, of Pay de Dome, France, after the termination of the World War, and returned to his work in Philadelphia.

He died at his home in Wynnewood, Pennsylvania, following a brief illness, on November 15, 1938. He is survived by his widow, a daughter, Jeanette, and a son, John Clark Keene.

Dr. Keene's untimely death came as a great shock to his many friends. His loss to the profession cannot be estimated, but he will always remain as a guiding star because of his professional and personal honesty, his ability and sincerity in his efforts to advance the sound principles of medicine.

Norris W. Vaux.

Original Communications

THE INCIDENCE OF ANOVULATORY MENSTRUATION AMONG PATIENTS OF LOW FERTILITY

JOHN ROCK, M.D., MARSHALL K. BARTLETT, M.D., AND DONALD D. MATSON, A.B., BROOKLINE, MASS.

(From the Fertility Clinic of the Free Hospital for Women)

FOR the solution of any problem of infertility, we attempt to examine the integrity of what we consider the six essential factors of fertility; namely, ovulation, spermatozation, insemination, conjugation, migration, and nidation. The proper fulfillment of all these functions is necessary for a normal human conception. Only two of them are easily examined, spermatozation and insemination. The quality of the other functions must be deduced from indirect evidence: migration (of both spermatozoa and zygote) by its possibility because of the patency of the cervix, uterus and tubes; conjugation, by the postponement of otherwise justifiably expected menstruation; normal nidation, by the further prolongation of amenorrhea and the absence of signs of ectopic gestation; and finally, ovulation, with which we are here concerned, by equally indirect methods as yet. The time seems fast approaching when we may have a direct and prompt index of ovulation, since Burr, Hill and Allen[1] have demonstrated ovulation in the rabbit by its electrical effect. As recently as June, 1937, Rock, Reboul and Wiggers,[2] adopting Burr's technique, obtained a similar electrical reaction in one woman, and in another woman such a sign was obtained by Burr[3] and his co-workers. Until this or some other method is perfected, we must depend in most cases on the older indirect means of deducing ovulation from demonstrable evidence of corpus luteum activity. Study of ovarian behavior in subprimate mammals justifies us in assuming such activity to occur only following normal ovulation. (The quality of the ovum, except as vouchsafed by this phenomenon, is beyond our examination.) The evidence of corpus luteum function is found in the endometrium, where progestin-specific changes have been described by many in this country as well as abroad. (Corner and Allen,[4] 1929; Bartelmez,[5] 1933; Rock and Bartlett,[6] 1937.)

Menstruation was formerly considered presumtive evidence of ovulation, but now we demand menstruation from a secretory mucosa as an indication. For clinical purposes we may demand even more than this, and consider effective ovulation to have taken place only if a corpus luteum effect is found to persist for a minimal period. Arbitrarily, we select ten days for this interval between the beginning of corpus luteum or progestin effect in the endometrium and menstruation.

NOTE: The Editor accepts no responsibility for the views and statements of authors as published in their "Original Communications."

MATERIAL AND RESULTS

This investigation of the frequency of anovulatory menstruation is based upon a study of biopsy specimens of the uterine endometrium obtained by the small suction curette from patients complaining of sterility. The advantages and limitations of the suction curette for study of the endometrium have been described by Klingler and Burch[7] (1932), Rock[8] (1934), Novak[9] (1935), Kurzrok[10] (1937), Rock and Bartlett[6] (1937), and others. It is emphasized that these biopsies may be repeated frequently, without anesthesia, as an office procedure, and are therefore adaptable to investigation of successive cycles or to study at intervals throughout a single cycle.

This report considers 392 patients upon whom biopsies were performed. In these cases the preceding and succeeding menstrual dates as well as the menstrual history of the patients are known. Repeated biopsies were obtained from a large proportion of them.

Thirty-six patients of this group showed evidence of anovulatory menstrual flow; that is, bleeding of normal duration from a nonsecretory endometrium at an interval of not less than three weeks from the previous menstrual flow, and not more than ten days after the biopsy was taken. All of these 36 patients showing evidence of anovulatory menstruation were within the childbearing age. Eighty-eight per cent of them were between 20 and 34 years of age and the remainder, between 35 and 39. The biopsies were taken as follows:

38 per cent on the day of flow;
35 per cent on the first or second day previous to the flow;
18 per cent on the third to seventh days previous to the flow;
9 per cent on the eighth to tenth days previous to the flow.

Only five biopsies are counted in this series, then, which were taken more than a week preceding the menstrual flow, and these were taken on the eighth, ninth, and tenth days. Biopsies taken more than ten days before the succeeding flow we believe should not be considered, because then the formation and regression of a functioning corpus luteum becomes possible, though such a sequence is probably not normal in less than twelve days. These findings indicate an incidence of 9.1 per cent of sterile women who show evidence of anovulatory menstruation.

Of these 36 patients, 18, or 4.6 per cent of all sterility patients in this series, showed evidence of anovulatory menstruation on more than one biopsy:

10 patients had 2 anovulatory periods
2 patients had 3 anovulatory periods
2 patients had 4 anovulatory periods
1 patient had 6 anovulatory periods
2 patients had 7 anovulatory periods
1 patient had 8 anovulatory periods

Eight of the patients, or 22 per cent, showing anovulation also showed bleeding from a secretory endometrium, definite evidence of ovulation, at a subsequent biopsy. Cases illustrating this combination of anovulatory with true menstruation are described below.

Since the clinical diagnosis of anovulatory menstruation would be of great significance in dealing with sterility patients, it is important to analyze the menstrual habits of this group and also of sterility patients in general.

TABLE I. RELATIVE FREQUENCY OF MENSTRUAL IRREGULARITIES AMONG STERILITY PATIENTS AND THOSE SHOWING ANOVULATION

TYPE OF MENSTRUAL ABNORMALITY	36 PATIENTS SHOWING EVIDENCE OF ANOVULATION	356 STERILITY PATIENTS
Oligomenorrhea	14 or 38.8%	35 or 9.8%
Amenorrhea	10 or 27.8%	11 or 3.1%
Irregular catamenia	8 or 22.2%	26 or 7.3%
Metrorrhagia	4 or 11.1%	41 or 11.5%
Polymenorrhea	3 or 8.3%	27 or 7.5%

Table I records the relative incidence of various types of menstrual abnormalities among the infertile patients who had at least one anovulatory period and among those in whom none such was discovered.

These figures indicate that a history of periods of amenorrhea is nine times as frequent in sterility patients showing anovulatory menstruation as in others; oligomenorrhea, four times as frequent; and irregular catamenia, three times as frequent; whereas a history of metrorrhagia and of polymenorrhea appears in both groups with about the same frequency.

While these results do not indicate that anovulatory menstruation can be diagnosed from the sterility patient's menstrual history, they are at least suggestive. We believe that with an infertile patient a history of periods of temporary amenorrhea, of oligomenorrhea, or of irregular catamenia should arouse suspicion of anovulatory menstruation and should indicate repeated endometrial biopsy studies through several menstrual cycles.

In addition to the group of 36 patients considered to have had an anovulatory period, there were 11 patients who bled from a nonsecretory endometrium but were not included in our series because the flow occurred less than three weeks after the preceding flow. Such flow in these patients is, probably, anovulatory, but we think does not merit the diagnosis of menstruation, because of the short interval between periods. Seven of these entered with a complaint of metrorrhagia, two complained of oligomenorrhea, one of polymenorrhea, and one of irregular catamenia. One of these patients, at a subsequent biopsy, showed evidence of ovulation.

Biopsies on another group of 15 patients, who are not included in our series because the dates of the preceding and following periods of flow were not definitely established, showed bleeding from a nonsecretory endometrium. In this group, twelve complained of metrorrhagia. The complaint and the findings on examination are both characteristic of dysfunctional uterine hemorrhage.

Seventy-seven biopsies were performed on 54 patients complaining of amenorrhea. Of these 54 patients, only eight showed secretory endometrium, while the remaining specimens were proliferative or hypoplastic. The subsequent history of 3 of the 8 patients is unknown. Of the other 5, all flowed in a few days. It is not to be assumed that biopsy precipitated a flow which would not otherwise have occurred, since in over 400 biopsies showing secretory endometrium only 4 did not flow in sixteen days, and two of these flowed in twenty days. We cannot explain this delay in menstruation except by postulating a short pregnancy, or by assuming the most unlikely phenomenon of a persisting corpus luteum spurium. It appears, therefore, that practically all patients, even those with a history of amenorrhea, once they do ovulate, will flow after an interval of not more than sixteen days, unless conception occurs. When the infertile cycle is lengthened, we believe it is due to a prolongation of the preovulative phase and not to the prolongation of the secretory phase, by persisting progesterone effect; for in the absence of pregnancy we find no evidence of what has been commonly referred to as a "persisting corpus luteum."

CASES OF REGULAR ANOVULATORY MENSTRUATION

Occasionally one finds a patient in whom the periodicity and amount of flow is such as to justify her belief that she is menstruating normally, but biopsy proves her flow to be anovulatory. The records of 4 such patients follow:

CASE 1.—The case of Mrs. B. (121-239) was reported by Rock and Bartlett.[6] This patient flowed four times with fair regularity after being amenorrheic for over a year. The first three bleedings were shown by biopsy to have occurred from proliferative endometrium. The fourth was not preceded by biopsy.

CASE 2.—Mrs. D. (140-204), 22-year-old nulliparous Italian housewife. Her periods began at 15 years of age, the interval was at first regular from thirty to thirty-two days and the flow lasted eight days. Subsequently, the flow became irregular, and was reduced to four days' duration. At one time she was temporarily

amenorrheic for three months. Fig. 1 demonstrates that in two series of visits to the clinic this patient showed 12 menstrual periods occurring with fair regularity. Seven of them were preceded by biopsies showing hypoplastic or proliferative endometrium, and 5 intercurrent periods of flow occurred without preceding biopsy, showing that the catamenias were not precipitated by this procedure. This patient flowed for over a year with only slight irregularity but was never found to ovulate.

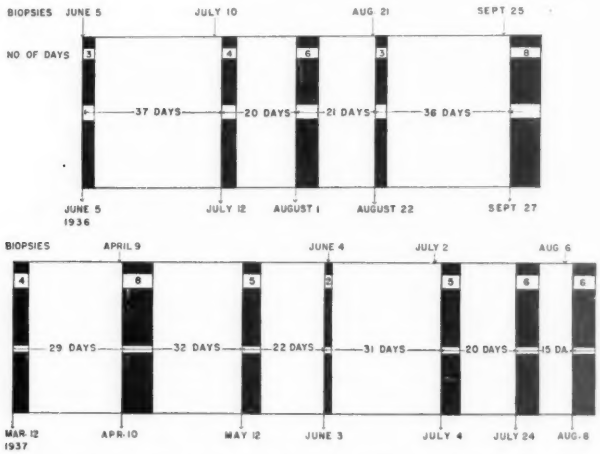

Fig. 1.—Anovulatory menstruation. Mrs. M. D. (140-204), aged 22 years. No labors. All biopsies showed proliferating endometrium.

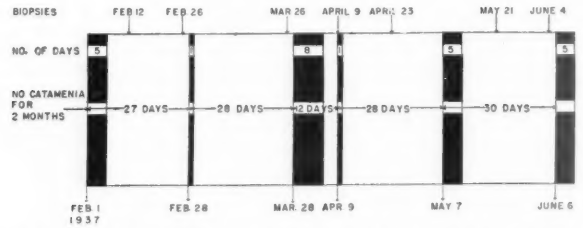

Fig. 2.—Anovulatory menstruation. Mrs. E. S. (82-28), aged 31 years. Labors none, miscarriages 4, irregular catamenia. All biopsies showed proliferating endometrium.

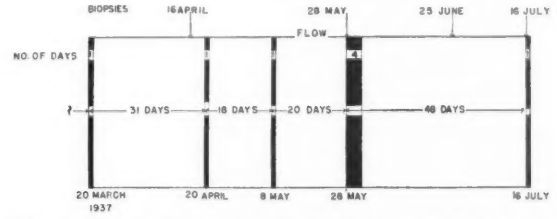

Fig. 3.—Anovulatory menstruation. Mrs. D. (146-141), aged 28 years. Labors none. Irregular catamenia. All biopsies showed proliferating endometrium.

Case 3.—Mrs. E. S. (82-28), a 31-year-old white housewife, with a history of four so-called miscarriages. Her periods began at 11 years of age, occurred at first every thirty days and then more irregularly. The flow usually lasted for four days. Fig. 2 shows the incidence of 6 periods of flow during four months, occurring with one exception at acceptably regular intervals. All biopsies showed proliferating endometrium in such time relation to succeeding flow as to rule out ovulation.

CASE 4.—Mrs. D. (146-141), a 28-year-old nulliparous, white housewife. Her periods began at 13 years of age and were regular, occurring every twenty-eight days, until four years before coming to the clinic. She usually flowed three or four days. Fig. 3 is a graph of 5 periods of scant flow in four months, three of which were preceded by biopsies showing proliferating endometrium.

CASES ILLUSTRATING BOTH ANOVULATORY AND OVULATORY MENSTRUATION

Eight of the 36 anovulatory patients were found by repeated biopsies also to flow after ovulation.

CASE 1.—Miss K. (140-100), who complained of polymenorrhea and dysmenorrhea, showed evidence of bleeding from both secretory and nonsecretory endometrium in 6 biopsies obtained at irregular intervals during six months:

DIAGNOSIS OF BIOPSY	DAY OF FLOW AFTER BIOPSY	CYCLE
1. 17-day	10th	ovulatory
2. Proliferative	7th	anovulatory
3. 18-day	6th	ovulatory
4. Proliferative	5th	anovulatory
5. 22-day	6th	ovulatory
6. 26-day	0	ovulatory

CASE 2.—Mrs. G. (131-356), a 23-year-old Italian housewife. Her periods began at 13 years and had been irregular with an interval usually longer than thirty days. She habitually flowed four days. In 1935 she flowed 5 times at fairly regular intervals of twenty-two to twenty-seven days, two of these catamenias being preceded by biopsies showing proliferative endometrium with dysplasia. These were followed by 5 months of amenorrhea during which two biopsies showed proliferating endometrium with dysplasia and one showed hypoplasia. Then the patient began to flow again at regular twenty-eight- to thirty-day intervals. Just before the fourth of these periods a biopsy showed typical secretory endometrium as did three more biopsies taken before succeeding periods. Apparently this patient, after an anovulatory interval of ten months, during part of which she was amenorrheic as well, suddenly commenced to ovulate again.

CASE 3.—Mrs. F. (137-278), who complained of periods of amenorrhea, showed evidence of anovulation and later proved she ovulated, once by biopsy and after that by becoming pregnant. The first biopsy was taken on the day she commenced to flow, after more than two months of amenorrhea, and showed late proliferative endometrium. Again she flowed two days after a biopsy showing late proliferative endometrium and twenty-nine days from the previous flow. Before the next biopsy was taken the patient had ovulated, for the endometrium obtained was characteristic of the fifth day of progestin influence and the menstrual flow followed in six days. Before the next catamenia the patient became pregnant.

DISCUSSION

The normal menstrual cycle of adult fertile human females is manifested in the uterine endometrium by a series of progressive changes culminating in the menstrual flow. These changes fall into two phases which correspond with ovarian endocrine activity: first, the proliferative stage under the stimulus of the estrogenic substances of the ripening follicle; second, the secretory stage characterized by glandular alterations and possibly secretion, and by stromal and vascular mutation under the stimulus of both the estrogenic and progestational principles

of the corpus luteum. In such a cycle, then, bleeding occurs from an endometrium built up under the stimulus of follicular hormones and subsequently modified by the hormones of the corpus luteum.

During the past decade, evidence has been accumulating from many sources that bleeding of such a character and duration as to be clinically indistinguishable from normal menstruation may occur from a non-secretory endometrium. Furthermore, the process of tissue destruction which eventuates in this form of uterine bleeding is not dissimilar to that which causes the shedding or deciduation of the normal predecidua.[6] Whatever the factors are which normally regulate the onset of the menstrual flow, it appears that the presence of the corpus luteum and with it the corresponding secretory or progestational transformation of the endometrium is not essential. Menstruation without preceding ovulation is probably a frequent occurrence at puberty, at the menopause, and in the post-partum period,[11] and apparently not infrequent among sterility patients during the childbearing age.

The first suggestion of anovulatory menstruation came from Heape[12] (1894; 1897) even before the time of ovulation was known at all. Heape collected menstruating uteri of *Semnopithecus* and *Macacus rhesus* monkeys and observed that very few of them were accompanied by ovaries which contained corpora lutea. Van Herwerden[13] (1905) reported observations on 87 Java *Macacques* among which two types of menstruating uteri were found: one with a narrow mucosa, resting glands and poorly developed vessels with which no corpus luteum was associated and a second type, with swollen mucosa, secreting glands and thick-walled vessels associated with a corpus luteum. This author postulated a breeding season during which menstruation was preceded by ovulation and a resting season when cyclical menstruation continued in the absence of ovulation.

The normal occurrence of anovulatory menstrual cycles in monkeys out of breeding season was firmly established by the work of several investigators in this country many years later. Corner[14] (1927), over a five-year period, found by repeated laparotomies and autopsies upon young mature female *Macacus rhesus* monkeys that menstruation occurred frequently when no corpus luteum could be discovered. However, he did conclude that when ovulation occurred in the monkey, the following menstruation seemed to come at a regular interval, about twelve to fourteen days. He described two types of bleeding endometrium, one showing proliferation only and the other progestational changes. Corner also cites isolated cases, including one observed by himself, of young women known to have had recent cyclic menstruation who were autopsied after death due to other causes and in whom no evidence of recent corpus luteum formation was found.

At this time, Allen[15] (1927) observed by correlating the number of regressing corpora lutea present with the preceding instances of menstruation in five monkeys, that ovulation occurred in less than 50 per cent of the cycles. Allen also found that menstruation occurred upon

the cessation of injections of lipoid extracts of ovarian tissue into spayed animals after a certain degree of growth had been induced by the injected hormone.

The overwhelming evidence of Hartman[16] (1932) definitely established anovulatory menstruation in the *Macacus rhesus*. He observed by numerous methods several hundred proved cases of menstruation without preceding ovulation and showed that in the monkey, ovulatory and non-ovulatory cycles were followed by approximately the same amount of bleeding.

The problem of anovulatory menstruation in the human female is a much more difficult one to investigate and conclusions drawn from comparisons with the other primates are not easy to evaluate. Novak[17] in 1930 raised the question as to whether certain pathologic forms of hemorrhage in the human being which may still retain a certain periodicity are not to be looked upon as analogues of menstruation without ovulation in the monkey. These instances of bleeding when ovulation does not occur, and in which there is almost always a characteristic hyperplastic nonsecretory type of endometrium, may be, he thought, instances of an occurrence which may not be infrequent. Novak proposed that dysfunctional uterine bleeding, seen so characteristically at puberty and the menopause, is to be considered as reversion to the follicular type of sex cycle seen in most of the lower animals, including some monkeys.

By 1934 Novak[18] was ready to assert beyond dispute that anovulatory menstruation occurs in some women. He says: "Functional menorrhagia, at times not very excessive, is characteristically associated with an anovulatory mechanism and undoubtedly it occurs in some cases in which the menstrual flow is within normal limits." Novak believes that the proportion of anovulatory cycles in normally menstruating women is very small but that in unexplainable cases of sterility it may be very high.

Experimental hormone injections by various workers have contributed materially to this problem. Following the preceding demonstrations of Clauberg[20] and Kaufmann,[21] those of Werner and Collier[22] (1933) are very significant. In four women showing endometrial atrophy following bilateral oophorectomy, large doses of theelin resulted in hyperplasia of the endometrium and repeated flow from the nonsecretory endometrium. All four patients bled during the injections and three, after the injections were stopped. Their bleeding was qualitatively indistinguishable from menstruation in normal women, though there was quantitatively less loss of tissue. The patients are also said to have experienced the symptomatology of menstruation. In these cases the absence of corpus luteum effect cannot be doubted. One of us[8] obtained similar results with two intact women whose ovaries were quite inactive.

Bartelmez[5] (1933) examined with great care a number of menstruating uteri obtained at operation. He found that various portions of the uterus respond differently to hormonal stimuli, a fact which we believe may account for many of the discrepancies found in reports upon endometrial specimens. As pointed out by Rock and Bartlett[6] (1937),

specimens taken from the mucosa high on the anterior or posterior wall of the fundus most consistently show the characteristic cytologic changes. Bartelmez concludes that the only invariable endometrial changes observed during menstruation are vascular. In his series he considers that he has one case with all the necessary data to prove anovulatory menstruation and four which suggest it.

Mazer and Ziserman[19] (1932) reported a series of 41 functionally sterile women subjected to premenstrual curettage among whom 24 showed a "non-nidatory" endometrium indicating defective luteinization or total absence of a corpus luteum. In our larger series of barren women so high a percentage was not found.

Anspach and Hoffman[23] in 1934 reported on 42 cases of apparently normal menstruation, 9 of which showed endometrium of the "interval," "hyperplastic," or "atrophic" variety, an incidence of over 20 per cent anovulatory menstruation, which again is a much higher percentage than was found in our series.

In contrast to these reports is that of the English investigator Shaw[24] (1934) who believes that it is probably very exceptional to find no corpora lutea in the ovaries of women who have menstruated regularly. He examined 30 specimens between the fourteenth and twenty-eighth days of the cycle and found them all to show secretory endometrium. He concludes that cyclical uterine bleeding is accompanied by ovulation and that bleeding independent of ovulation should be looked upon as so definitely pathologic, as not to be dignified with the term "menstruation."

Another English observer, Jeffcoate[25] (1935), in a series of 63 specimens from uteri obtained at operation between the twenty-first and the twenty-eighth day after the last period, in infertile subjects with regular cycles, found 16 which showed no evidence of luteal influence. This indicates an incidence, again, of 25 per cent anovulatory menstruation among sterility patients, a figure far in excess of our findings. In Jeffcoate's specimens, of course, the actual date of the following menstruation was not obtainable: a significant criticism which applies to all the cases in which specimens were obtained from extirpated uteri. Jeffcoate also examined by curettage the endometrium of 21 women who were supposedly in the premenstrual or menstrual period and found that 10 (or 48 per cent!) showed no sign of secretory activity. Because of the known variability of the preovulatory phase, this finding alone cannot be considered evidence of anovulatory menstruation.

In 1935, Bland, First and Goldstein[26] in this country reported the following results upon premenstrual curettage of 50 regularly menstruating sterile women: Premenstrual endometrium, 23; interval endometrium, 15; hypertrophic endometrium, 9; atrophic endometrium, 3. In other words, less than 50 per cent of this series showed endometrial evidence of corpus luteum activity. They state that in the cases of interval, hyperplastic or atrophic endometrium, "should fertilization occur the endometrium is not prepared to retain the embryo, and

abortion inevitably results.'' We do not believe that in these cases fertilization is even possible, for without the premenstrual changes in the endometrium, the release of a fertilizable ovum must be considered most unlikely.

The most recent series of cases reported is that of Mazer, Israel and Kacher.[27] They found that 19 out of 65 selected functionally sterile women showed no evidence of the secretory phase in uterine curettings taken one to six days before the expected menstrual flow, from which they conclude that ''cyclic uterine bleeding, clinically indistinguishable from normal menstruation, from an endometrium totally lacking the usual secretory changes, occurs in 30 per cent of sterile women who present no abnormality.'' These authors prefer the term ''pseudomenstruation'' to ''anovulatory menstruation'' when the diagnosis is based on endometrial findings alone since they believe that anovulation cannot be proved without concomitant study of the ovaries. We, however, have assumed that the presence or absence of secretory endometrium in the suction biopsy indicates the presence or absence of a functioning corpus luteum. Again as with the figures of Mazer and Ziserman,[19] of Anspach and Hoffman,[23] of Jeffcoate,[25] and of Bland, First and Goldstein,[26] we fail to find so high a percentage of cases of anovulatory menstruation.

SUMMARY AND CONCLUSIONS

1. Endometrial biopsies obtained by the small suction curette provide a useful and adequate means for determining the occurrence or failure of ovulation.

2. The diagnosis, anovulatory menstruation, should be distinguished from that of intermittent and irregular bleeding, better termed metrorrhagia.

3. In a series of 392 women complaining of sterility, about whom adequate information was available, 9.1 per cent showed evidence of at least occasional anovulatory menstruation.

4. About 4 per cent of sterility patients may be considered habitually anovulatory, because, for at least several months, they exhibit regular menstrual flow which is clinically indistinguishable from normal menstruation, but which comes from a proliferating or a hypoplastic endometrium.

5. Patients who usually flow regularly from a normal secretory endometrium may occasionally flow from a persisting proliferative endometrium.

6. Sterility patients with a history of menstrual irregularities, even though flowing normally at the time of examination, should arouse suspicion of anovulatory menstruation since such a failure of ovulation is three to nine times more frequent among these patients, than among those whose menstrual history is normal.

7. Anovulation and amenorrhea are commonly coexistent. Anovulation and regular or slightly irregular menstruation are occasionally co-

existent. Ovulation infrequently occurs in patients who are habitually amenorrheic.

8. A brief review of the literature on anovulatory menstruation is presented.

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THE DEGREE OF NORMAL MENSTRUAL IRREGULARITY*

An Analysis of 20,000 Calendar Records From 1,500 Individuals

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IT IS a traditional medical teaching that women usually exhibit a regularly spaced menstrual rhythm. That this belief still reflects accurately the opinions of many obstetric and gynecologic authorities is shown by their published statements. Representative lists of such textbook references have been given by Fluhmann (1934) and by Gunn and others (1937); it would be easy to extend these citations. Moreover, one is safe in asserting that it is the custom, both in better hospitals and private practices, to assume the normality of menstrual regularity as the basis of clinical questioning for case history purposes.

The commonest source of information from which judgments concerning menstrual periodicity have been derived is the hospital case record. As typical examples may be cited the extensive compilations by Sanes (1916) in this country, Nakagawa (1931) in Japan, Kennedy

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(1933) in Scotland, and Hajek (1933) in Czechoslovakia. Characteristic of this kind of inquiry is the conclusion of Nakagawa that 97 per cent of this group of 2,080 selected women menstruated regularly, or that of Kennedy who credits 75 per cent of 9,768 patients with having a regular twenty-eight-day cycle. The uncritical attitude customarily exhibited on these matters is well illustrated by Knaus (1934), who, bent on doing a bit of special pleading for his "safe period," explains away Kennedy's high (sic!) percentage of irregularly menstruating women on the basis of the group being drawn from gynecologic patients and not from a normal, healthy population. It is also Knaus who was irked by Fraenkel's well-known paradox concerning the irregularity of the menstruating woman ("Das einzig Regelmässige an der Regel ist ihre Unregelmässigkeit") into stating that he was "not prepared to settle this very important question in quite such an airy fashion without any foundation of fact"; whereupon he proceeded unquestioningly to accept, as the foundation stone of his theory, tabulations from routine hospital histories!

Historically fundamental to a popular belief in a regular twenty-eight-day cycle is the world-wide tradition of lunar influence. This superstition has been fostered through the influence of Arrhenius (1898) and has been credited by De Lee (1934) and others. However, Gunn, Jenkin and Gunn (1937), using reliable menstrual data, find no justification for associating the date or rhythm of menstruation with lunar phenomena; they are also able to show how Arrhenius reached his conclusions through the use of wholly unreliable data. In addition, it is now sufficiently established that an abetting factor that has done much to confuse the true picture of menstrual periodicity is the utter unreliability of woman's unaided memory in these matters. Her testimony may not even be consistent on different occasions of questioning (Sanes, 1916). Moreover, even if woman's memory concerning her own menstrual history were trustworthy, the mere method of approach by which menstrual histories are customarily obtained for clinical records would still load the scales against the truth: the questioner suggests by implication the "normal" reply expected; the patient senses that any other answer will mark her as atypical, and so reacts instinctively in a protective manner; the easiest way for her to avoid further discussion of an often embarrassing and seemingly inconsequential topic is to give the answer suggested, and especially so since "regularity" is entirely a relative measure that depends upon personal standards of interpretation.

For these reasons the analysis of accumulated hospital records is fruitless, while the numerous published articles dealing with menstrual periodicity, which have been based on these records, are without value. Only data taken from actual calendar records of women who are interested and responsible (or otherwise are adequately supervised) are acceptable for serious consideration. Fortunately there is a limited number of studies, published mostly within recent years, which make available the lengths of consecutive menstrual cycles as recorded by selected women over different periods of time. The general trust-

worthiness of these data has been reasonably safeguarded by various means and it is believed they are, on the whole, as accurate as may well be expected under such circumstances. It is the purpose of the present article to select and assemble these data, to subject them to statistical methods of analysis, and to reinterpret them both as individual studies and as a composite group. In this way it seems possible to bring to a conclusion certain fundamental inquiries regarding menstrual periodicity. This does not imply that the further collection of menstrual data is not badly needed. On the contrary, it merely signifies that the time has come to close certain of the simpler problems whose answers are sufficiently at hand and to direct future energies into resolving those other features of the menstrual function on which exact information is still lacking. For example, rather than to collect further quantities of short records, it will be far more profitable to seek out long-term menstrual histories and subject them to analysis. Richards (1935) and Hartman (1936; 1937) have already made a start in this direction, while the present writer will soon contribute also to this phase of the menstrual problem.

Some of the published menstrual data present the detailed records of the actual participants; other sets of data conceal this individual information and, instead, combine the cycles of all participants into one group. In a corresponding manner, the conclusions given sometimes represent generalizations drawn from individual records and averages, while in other instances the massed cycles of all individuals have been treated as though emanating from a mythical "average woman." On the whole, the former treatment is more exact and instructive, although certain valuable facts, as well, do come out of merged data. As a practical matter it has been necessary, in every instance but two, to accept the data as printed and to make the best of them in that form.

THE DISTRIBUTION FREQUENCY OF MENSTRUAL CYCLES

Some worth-while information can be gained by arranging the data to show the distribution frequency of all the cycle lengths encountered. In Table I this has been done for nine studies on adults and one on pubertal girls. All these subjects were white inhabitants of the north temperate zone; further details pertaining to the several sets of data are listed in Table III, but here it is only necessary to state that the participants were all supposedly healthy, or at least without conflicting pelvic disease. As may be seen, the modes for the several adult groups are divided evenly over 27, 28, and 29 days; the grand mode, both for adult women and for girls, is set at 28 days.* In the adults this value is clearly established, while for pubertal girls there is little supremacy of 28 days over 26, 27, and 29 days. Although the recorded cycle lengths

*In contrast to the facts embodied in Table I it is enlightening to compare the recent conclusions of Hajek (1933) who relied upon the verbal testimony of 1,480 women as recorded in case histories at the polyclinic at Prague. He credits 82 per cent as being "regular." Of the whole number 56.7 per cent reported a 28-day cycle, while only 0.6 per cent and 0.06 per cent claimed 27- and 29-day cycles, respectively. The neglect of 27 and 29 days in these histories shows how small is the reliance that can be placed on the details of histories given from memory.

TABLE I. DISTRIBUTION FREQUENCY, ACCORDING TO LENGTH, OF 5,322 MENSTRUAL CYCLES EXPERIENCED BY 485 ADULT WHITE WOMEN, AND 3,140 CYCLES EXPERIENCED BY 100 PUBERTAL GIRLS. THE MODAL VALUES ARE INDICATED BY ITALICS

SOURCE OF DATA	NO. OF SUBJECTS	NO. OF CYCLES	LENGTH OF CYCLES IN DAYS																					
			7-10	11-15	16-20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36-40	41-50	51-100	101-256
1. Issmer, 1889	12	120			2	2	1	1	5	9	14	17	*22*	19	13	6	3	3			3			
2. Latz and Reiner, 1935	102	1,113		1	4	1	8	22	45	101	127	152	*202*	119	87	80	62	31	25	16	25	4	1	
3. Latz and Reiner, 1937	100	1,336			4	5	18	46	84	133	175	*218*	209	158	114	75	36	22	14	4	11	7	2	1
4. King, 1926	17	523			1	1	11	16	43	60	66	*97*	76	50	37	23	11	6	6	7	5	6	1	
5. King, 1933	37	354			4	3	11	10	23	25	33	*51*	36	45	36	15	20	15	6	5	7	6	3	
6. Scipiades, 1935	47±	319						3	15	12	18	25	36	*49*	36	17	32	24	9	11	16	11	5	
7. Allen, 1933	44±	511			13	8	10	15	28	46	57	55	55	*61*	60	50	20	15	13	5	20			
8. Fluhmann, 1934	76	747		10	33	17	16	28	34	36	52	60	72	*73*	57	47	37	32	24	17	50	29	18	5
9. Pratt and others, 1929	50	299			1	4	8	22	33	33	43	37	*50*	20	16	19	5	3	3		2			
10. Engle and Shelesnyak, 1934	100	3,140	14	51	166	102	135	140	146	164	191	193	*202*	193	183	150	114	105	86	69	224	199	278	35
1-8. Totals, adults	485	5,322		11	62	41	83	163	310	455	565	712	*758*	594	456	332	226	151	100	65	139	63	30	6
10. Totals, pubertal girls	100	3,140	14	51	166	102	135	140	146	164	191	193	*202*	193	183	150	114	105	86	69	224	199	278	35

of the adult women run from 11 to over 100 days,* most of the entries lie between 25 and 31 days. The greater variability shown by pubertal girls, before the menstrual function has been smoothly established, is not unexpected.

It is instructive to compare some similar data on Japanese women as combined from studies by Obata (Ogino, 1934) on 959 students (number of cycles not given), by Ogino (1932; 1934) on 694 healthy multipara (883 cycles), and by a woman's journal (Fujin-Koron; Ogino, 1934) which collected 1,665 cycles (number of subjects not given). For this group two of the component curves have a 31-day mode while the remaining mode is at 32 days. The combined data show a mode of 31 days. The majority of entries are within the limits of 27 and 34 days.

Table I does not support the existence of favored subordinate types of cycle length (*e.g.*, 14-, 21-, 35-, 42-day), as have so long been described and even credited by recent authorities (*e.g.*, Novak, 1922).† It contrasts sharply with Kennedy's (1933) conclusions, drawn from the verbal testimony entered in 10,000 hospital records, in which these seven-day stages are strongly stressed. Yet in the combined Japanese data it is of interest to find that at weekly intervals of 21, 28, 36, and 42 days there are slight elevations which disturb the otherwise even distribution. This is chiefly caused by corresponding irregularities in Ogino's curve on multipara. Such occurrences at regular weekly intervals could not appear fortuitously; either they are real features of the menstrual phenomenon in these women or they are due to bias or error on the part of those furnishing the data. The fact that the curve for white women, known to be carefully collected, shows no similar tendencies and that the other two component Japanese curves largely lack this feature make one suspicious that such rhythmic disturbances in this instance are without real significance. They could easily result from the inclusion of records which tend to approximate round numbers in terms of the nearest week. An inquiry conducted on 6,000 school girls by the London Association of the Medical Women's Federation (1930) shows the predilection for whole weeks resulting from oral testimony. Similar tendencies appear in hospital records, as is shown by the figures of Nakagawa (1930), Hajek (1933) and Kennedy (1933).

Another way of handling the distribution frequency is to use the mean or modal cycle length characteristic of each person involved. This has the advantage of showing the distribution according to individual performance rather than as massed data in which individual peculiarities are lost. In many respects the modes would seem to be the more significant of the two. Practically, however, the data available for analysis are often too limited to show a reliable mode that can be taken as truly characteristic.

Of the several studies listed in Table I, those of Pratt and others (1929), Allen (1933), and Scipiades (1935) lack the information necessary for establishing individual modes. For the remaining sets of data, the group modes, expressing the greatest frequency of the individual modes, can be listed as follows: King (1933), 27 days; Latz and Reiner (1937), 27 days; Issmer (1889), 28 days; Latz and Reiner (1935), 28 days; Fluhmann (1934), 29 days; Engle and Shelesnyak (1934), 29 days. It is interesting that, except for the group of pubertal girls, these modes duplicate those for the mass distribution of cycles as shown in Table I.

*There are only a few scattering entries below 20 and above 50 days, except for 55 entries from Fluhmann's (1934) group of nurses. Perhaps Allen's (1933) data for nurses would also have been well represented in these extreme cycle lengths had the information not been lost (footnote ‡, Table IV). It is a question whether some of these long intervals should not be considered amenorrheal and hence be excluded from normal courses, even though Fluhmann tried to eliminate abnormal subjects (p. 22).

†Papanicolaou (1933) and Gunn (1937) have cited various writers who advocate the existence of menstrual types based on multiples of seven days. Papanicolaou, himself, holds for a rarer 21-day cycle, which is a fundamental mammalian type, and a commoner, longer cycle (usually 28 days) which includes a double uterine cycle.

TABLE II.* DISTRIBUTION FREQUENCY, ACCORDING TO AVERAGE LENGTH OF MENSTRUAL CYCLE, OF 1,165 ADULT WOMEN (14,512 CYCLES) AND 100 PUBERTAL GIRLS (3,140 CYCLES). THE MODAL VALUES ARE INDICATED BY ITALICS

SOURCE OF DATA	NO. OF SUBJECTS	NO. OF CYCLES	LENGTH OF AVERAGE CYCLE IN DAYS																		
			16-20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36-40	41-50	51-100
1. Issmer, 1889	12	120								2	*9*	1									
2. Latz and Reiner, 1935	102	1,113				1	3	5	15	*17*	*17*	13	8	11	9		2	1			
3. Latz and Reiner, 1937	100	1,336				1	8	7	13	*25*	15	14	9	5	2					1	
4. King, 1926	17	523						1	3	3	2	*5*	2						1		
5. King, 1933	37	354					2	3	2	5	4	*8*	5	2	1	2	2	1			
6. Gunn, et al., 1937	770	10,000±	2	4	8	26	57	94	112	*116*	100	74	54	38	24	17	13	6	15	7	3
7. Scipiades, 1935	51	319	1		1	2	1	3	6	2	10	*11*	1	2	4	1	2		2	1	1
8. Fluhmann, 1934	76	747	1	1	2	1	1	3	7	5	7	7	*11*	4	6	5		2	5	4	4
9. Engle and Shelesnyak, 1934	100	3,140				2	1	2	4	3	6	9	*10*	*10*	9	8	2	7	15	9	3
1-8. Totals, adults	1,165	14,512	4	5	11	31	72	116	158	*175*	164	133	90	62	46	25	19	10	23	13	8
9. Totals, pubertal girls	100	3,140				2	1	2	4	3	6	9	*10*	*10*	9	8	2	7	15	9	3

*The exact number of cycles collected is not given by these authors beyond the general statement that: "The investigation was planned to obtain one year's data from each individual." However, it is evident from the text that some subjects furnished more data than this (their Tables II and III). Since Gunn and his co-workers considered all average cycle lengths of, for example, 28.0 to 28.9 days as being 28 days, their distribution frequencies are not entirely comparable to those used by the present writer who has listed averages between 27.5 and 28.4 as 28 days. To make Gunn's distribution approximate the others in the present table, half of the individuals constituting each entry have been dropped back to the day previous.

TABLE III. GENERAL DATA CONCERNING MORE THAN 15,500 MENSTRUAL CYCLES FURNISHED BY 1,189 WOMEN AND GIRLS

SOURCE OF DATA	NATIONALITY	OCCUPATION	NO. IN GROUP	AGE RANGE AT START (YEARS)	MEAN AGE (YEARS)	TOTAL NO. OF CYCLES	RANGE IN NO. OF CYCLES REPORTED	MEAN NO. OF CYCLES PER PERSON	SHORTEST AND LONGEST CYCLE (DAYS)
1. Foster, 1889	American	Selected patients	56	----	----	330	5; 18	6.8	16; 46
2. Issmer, 1889	German	Housewives	12	19-39	26.8	120	10; 10	10.0	20; 40
3. Latz and Reiner, 1935	American, Canadian	Housewives	102	20-45	31.0	1,113*	6; 44	10.9	15; 51
4. Latz and Reiner, 1937	American, Canadian	Housewives	100	21-49	31.7	1,336	7; 49	13.4	19; 101
5. King, 1933	American	Industrial workers	21	17-35	23.3	161	4; 13	7.7	16; 57
6. Gunn, et al., 1935	British	Professions	479	13†-51	27.3†	6,000†	----	13.0†	----
7. King, 1926; 1933	American	College women	33	17‡-35	23.8	716	3; 104	21.7	18; 53
8. Scipiades, 1935	Hungarian	University students	50	18-34	24.5	339§	----	6.6	20; 91
9. Pratt, et al., 1929	American	Nurses and office workers	50	12-36	----¶	299	----	6.0	19; 36
10. Allen, 1933	American	Student nurses	110	----	----	1,291	----	11.7	13; 84
11. Fluhmann, 1934	American	Student nurses	76	18-27	20.4	747	3; 19	9.8	11; 144
12. Engle and Shelesnyak, 1934	Jewish-American	Orphanage inmates	100	11-15	13.1	3,140	20; 69	31.4	7; 256
1-11. Totals, etc. (adult groups)			1,089	12-51	26.1	12,452	3; 104	10.7	11; 144
12. Totals, etc. (pubertal girls)			100	11-15	13.1	3,140	20; 69	31.4	7; 256

*Seven cycles have been omitted from the record of Subject 149 in the original report. These cycles are atypically long and there is an accompanying notation that the individual was suffering from an ulcer of the stomach during this period.

†Only six individuals were under 18 years of age. The average age, total number of cycles and mean number of cycles furnished by each person are approximations deduced from the incomplete data as furnished.

‡The record of one individual included 24 cycles starting from the time she was 13½ years old. After a break of eight years the record was resumed. These earlier cycles have been included in the computations, since, strangely enough, they are not inconsistent with her later rhythm.

§Although the total number of cycles is stated to be 386, a smaller number (339) is actually used in the detailed analysis given. There are some additional discrepancies and suppressions in the handling of these data so that no mathematical treatment can be perfectly consistent or quantitatively exact.

¶See p. 21, last paragraph.

The distribution according to the mean cycle length of individuals is presented in Table II. This information was obtainable from eight groups of adults and one group of pubertal girls. As with the distribution of modes, just discussed, this style of tabulation permits the menstrual tempo of individuals to show as entities. In five of eight groups where direct comparisons can be made with Table I there is a shifting of the group modal values; yet the decisiveness of the grand mode for the combined groups is changed but little. The grand mode of the means of all adults is 27 days, while the corresponding grand mode of the pubertal group is shared by 30 and 31 days. Again, any evidence for favored types, spaced at weekly intervals, is lacking and the distribution curve throughout approximates the even form customarily considered normal.

DETAILED ANALYSIS OF GROUP DATA

The distribution curves, shown in Tables I and II, theoretically might be produced either by closely spaced, individual records which are highly regular or by overlapping records of considerable individual variability. In order to ascertain which possibility is correct one must scrutinize individual records, accurately kept. Yet it is remarkable how few of these have been collected until recently. Scientific curiosity was quick to invade almost every aspect of human behavior, yet it long neglected this most obvious one. Menstrual regularity has been so thoroughly assumed that only a few persons have ever thought it worth while to gather reliable information through the medium of actual calendar records. All of the contributions of this sort which I have been able to discover are reviewed in the paragraphs which follow. In order to make the several studies more easily compared, some of their general data have been assembled as Table III. This tabulation, like those which follow it, has been prepared by working over the raw data of the original papers and adding, where possible, other desirable information obtained through correspondence with the authors. In this way the data have been corrected and altered in some instances, while in others they have been made more complete than the original publications show. Some apparent disagreements with the original publications are due to errors which exist in those communications but which have now been eliminated. The following notes supplement Table III by presenting certain information, mostly of a general nature, not amenable to tabulation.

The factual attack on the problem of menstrual regularity is not altogether new.

As long ago as 1889 Foster reported on 56 New York women, 20 of whom had at some time been pregnant, under his observation for various affections. Having included only those whose ailments were not accompanied by disordered menstruation, he obtained calendar records of 5 to 18 periods from each participant. The cycles ranged from 16 to 46 days in length. One patient reported perfect regularity throughout her period of observation, but the length of this span was not given. The cycles of the remainder showed a maximum variation of 1 to 18 days from a 28-day norm, although whether this departure was from the group mean or from an arbitrary 28-day standard is not now determinable. It is interesting to read the discussion which followed the presentation of this report; several clinicians maintained that such widespread irregularity must have been due to pathologic conditions. Even today, nearly fifty years later, similar comments are being made on similar occasions!

In the same year Issmer (1889) in his noteworthy contribution on the duration of pregnancy included the menstrual records of 12 Bavarian housewives for ten

months preceding pregnancy. The shortest cycle was 20 days and the longest 40 days, while no person was regular in the menstrual function. The maximal departures from individual means ranged from 2 to 12 days.

These two reports should have opened the eyes of physicians to the desirability of collecting additional information, but they were without appreciable effect and the time-honored faith in normal menstrual regularity continued to dominate clinical thought. Hence one must pass over an interval of some forty years before the next serious contribution appeared. This study was made by King (1926; 1933), but before considering her investigations in detail it may be simpler to continue with some other reports made on women drawn from the general population.

Somewhat comparable to Foster's original material was a heterogeneous group observed by Geist (1930). His brief report covers 200 women who kept records for one year. Most of these were patients, who, though not actually ill or suffering from pelvic disease, were under observation for various reasons. Those women who had previously declared their periods occurred on a specific day found themselves in error. "In most instances, however, there were variations . . . from five days before the accepted time to ten days after, and this variation occurred almost as frequently as would the so-called normal cycle." In a few individuals 28-day periods were experienced for nine of the twelve months and in some others there was extreme irregularity for six to seven months and then suddenly a return to a 28-day cycle for the rest of the year. No other details are given in this report, and, unfortunately, attempts to supplement these meager facts through correspondence have been unsuccessful; for these reasons it is not possible to include Geist's results in Table III or to consider them further for detailed analysis.

Two other sets of data drawn from the general population have recently been published by Latz and Reiner (1935; 1937). Included are 2,449 cycles which 202 women from various parts of the United States and Canada had recorded on calendars and sent these authors in the hope of establishing their ovulatory rhythm. Although unsupervised, it would seem that the purpose (contraception by the "natural method") for which the data were collected should have been a sufficient incentive to insure accuracy. Yet to a certain degree these records are selective and show a greater regularity than the average; especially do women who are so irregular that they feel they cannot use the method, fail to submit their records (private communication). In any event, the cycle lengths given range from 15 to 101 days, no record is regular, and the maximum departures from individual means vary from 1 day* to 53 days. In numerous instances notations of illness (including colds), fright, abortion, mental stress, physical strain, change of climate, etc., are recorded as accompanying unusually long or short cycles. If these cycles are removed as atypical, as Latz believes they should be (private communication), then the regularity increases appreciably. Latz and Reiner conclude that 90 per cent of women show a range of variation not exceeding eight days and that 80 per cent of all women menstruate regularly enough to make safe use of the Ogino-Knaus sterile period. Bartelmez (1937) has commented on the 1935 publication as follows: . . . "by excluding all relatively long or short cycles which could possibly be attributed to external influences like emotional upsets, infections, etc., and by an ingenious method of grouping his cases, [Latz] endeavors to minimize the extensive variability observed."

Part of King's (1933) study, already mentioned, was devoted to a report on 21 women engaged in industry at Rochester, N. Y., and Baltimore, Maryland. A total of 161 recorded cycles was collected, but difficulty was encountered with these women in maintaining a sustained interest in the keeping of proper records; this is shown by the fact that 11 individuals supplied not more than five cycles each. None was regular. The maximum departures from individual means ranged from one day (only five cycles recorded) to 26 days. Considering the small number of cycles per person, the variability shown is considerable.

*One exceptional record shows 9 out of 11 cycles as 28 days long and the other two as 27 days. The subject had been mentally deranged some years before; hence one wonders at the trustworthiness of this sequence even though it is possible to find segments of long-term menstrual records that approach this one in uniformity.

The other homogeneous group of women studied by King (1926; 1933) consisted of 33 Baltimore college undergraduates, graduate students, and instructors who supplied information concerning 716 cycles. The range of cycle lengths extended from 18 to 53 days and no individual was regular in any true sense over her respective observation period. The maximum variations from individual means varied from 2 to 20 days.

On the whole, the younger members (17 to 19 years) listed in King's tables show definitely more erratic records than do the older women. A greater variability in adolescents, before the rhythm is well established, has been mentioned by various writers, yet the exact degree of such variability remained unknown until Engle and Shelesnyak (1934) recently investigated this matter. They have published data obtained from 100 pubertal girls of a Jewish orphanage under conditions which should guarantee the accuracy of the records. At least 20 periods were obtained from each girl. The range in length of all cycles varied from 7 to 256 days, and the individual variability was high, as well. Although 28 days is the mode of all the cycles as a group, it is actually modal for only eight of the hundred individuals. Irregularity was found to decrease as menstrual experience increased. At the end of the first 20-24 cycles (mean terminal age, 15.5 years) the average standard deviation from the individual means was ±20 days. Thereafter, there was a progressive trend toward regularity; for example, when 40 to 44 cycles had been experienced (average terminal age, 16.4 years) the standard deviation for the total period since menarche was reduced to ±10 days. Ball (Hartman, 1936) also found a great irregularity in a study of adolescent girls at a state school near Baltimore. Hartman (1936) has emphasized this matter in an interesting and significant way by publishing beneath Ball's distribution diagram a second diagram, based on adolescent monkeys, which is strikingly similar.

Another study limited to college students (of philosophy and medicine), resident in university buildings, has been made by Scipiades (1935) at Budapest. Fifty women furnished data for eight months. No person was found to be regular; the extreme conditions are shown by two individuals who maintained their means in 43 per cent of their recorded periods and 38 women who on no occasion experienced their means.

It is possible that clinical patients, such as those previously mentioned, do not present ideal material for menstrual study, yet it must be admitted that their variability is no greater than in the college type just described. More pertinent are the objections which have been advanced against the representative nature of certain menstrual data obtained from nurses' training schools. This is because it is held as a well-recognized fact that a nurse's mode of life is conducive to marked menstrual irregularities and even to indefinite periods of amenorrhea.

Not admitting the validity of this criticism, Allen (1933) studied a group of student nurses at Chicago. The individuals were unselected, but detailed consideration may be limited to 110 whose 1,291 cycles were said to have been strictly controlled through a diligent, personal check-up prosecuted by the supervising nurse at the time of each expected monthly report. No subject proved to be actually regular, one in four was "absolutely irregular," while the extremes of cycle length ranged from 13 to 84 days. The six detailed, individual records which Allen gives as typical samples show great irregularity. It is of interest that 87 nurses, who at the beginning believed in their perfect regularity, actually were marked irregular. Fifty-three recognized that they were somewhat irregular but were astonished by the degree of irregularity brought to light.

More fully presented were the results furnished by Fluhmann (1934) on 76 California student nurses. It is possible that these subjects were better selected than Allen's, inasmuch as an elimination was made of individuals who were adjudged to show signs of menstrual disturbances due to the influence of their changed environment. A total of 747 cycles was collected over a period ranging from 6 to 13

months. The cycles varied from 11 to over 144 days in length, but 97 per cent of them were between 18 and 42 days long. The total spread was definitely more divergent than the corresponding values in Allen's series. Only five women kept within a five-day range between their shortest and longest cycles. Perhaps the relative youth of these nurses conspired with an occupational influence to produce this seemingly excessive irregularity.

Less homogeneous is a group of 50 nurses and office workers at Detroit who furnished 299 cycles, as described by Pratt and his associates (1929). At the start all considered they had regular periodicity. Yet when the records were finally disclosed, each was astonished at finding herself to have been in error. This group unfortunately consists of a mixture of adolescents and adults. Since the original records were not preserved it is not possible now to state what the distribution according to age actually was. In a letter, Dr. Pratt has written as follows: "None

TABLE IV. DETAILED DATA PERTAINING TO 8,812 MENSTRUAL CYCLES FURNISHED BY 644 WOMEN AND GIRLS. ALL THE CYCLES OF EACH GROUP WERE COMBINED AND TREATED AS IF BELONGING TO A SINGLE INDIVIDUAL

SOURCE OF DATA	MODAL CYCLE LENGTH (DAYS)	MEAN CYCLE LENGTH (DAYS)	AVERAGE DEVIATION OF CYCLES FROM GROUP MEAN (DAYS)*	STANDARD DEVIATION OF CYCLES FROM GROUP MEAN (DAYS)	PROBABLE ERROR OF STANDARD DEVIATION (DAYS)	CO-EFFICIENT OF VARIATION	PROBABLE ERROR OF CO-EFFICIENT OF VARIATION
1. Foster, 1889	--	28.0†	----	----	----	----	----
2. Issmer, 1889	28	27.8	2.09	2.93	0.13	10.54	0.46
3. Latz and Reiner, 1935	28	28.4	2.34	3.27	0.05	11.51	0.12
4. Latz and Reiner, 1937	27	27.3	2.21	3.65	0.05	13.37	0.17
5. King, 1933	27	29.1	3.13	5.46	0.21	18.77	0.71
6. King, 1926; 1933	27	27.7	2.59	3.68	0.07	13.29	0.23
7. Scipiades, 1935	29	30.2	3.42	7.17	0.19	23.74	0.63
8. Pratt, et al., 1929	28	26.6	2.22	2.81	0.08	10.56	0.29
9. Allen, 1933‡	29	28.2	2.89	3.77	0.08	13.37	0.28
10. Fluhmann, 1934	29	30.4	5.83	11.58	0.20	38.09	0.66
11. Engle and Shelesnyak, 1934	28	33.9	10.48	11.80	0.10	34.83	0.30
1-10. Means for adults	--	28.4	2.97	4.92	0.12	17.03	0.39
11. Means for pubertal girls	28	33.9	10.48	11.80	0.10	34.83	0.30

*In calculating the average deviations, the mean cycle length of each group was reduced to the nearest whole number (e.g., 27.5–28.4 was considered to be 28).

†It is impossible to decide what Foster meant by a 28-day mean; perhaps his statements merely refer to the 28-day standard so thoroughly assumed at that time. Hence the percentages in the first three columns of Table VI are given with reference to this 28-day average, whatever it may imply.

‡Some error has crept into Allen's work. Although 1,291 accurate periods were collected, only 511 (ranging from 17 to 40 days) were actually summarized in his Table III. It is obvious that the ones omitted from the ends of his series, which actually extended from 13 to 84 days, can account for but few of the missing 780 entries. In a personal communication Dr. Allen suggests that many of the original slips may never have been recorded on the permanent record and this loss was not detected subsequently. He believes from memory that the entries in his Table III are representative and it is these data that have been used for the details entered in Tables IV to VI of the present report. One can calculate proportionately that these 511 cycles were drawn from about 44 nurses. On the other hand, the more general data of the present Table III pertain to the full group of 110.

of the records included first menstruations. Most of the records were taken between the ages of 16 and 25.'' But since marked irregularity is a characteristic of the adolescent and is still pronounced at the nineteenth year (Table VII), one would expect part of the results to be as they are. The really significant feature, however, which gives this report value, is that all participants, regardless of age, were irregular.

The most recent publication on menstrual periodicity is by Gunn, Jenkin and Gunn (1937). This is the fullest and most careful investigation yet conducted on adults. A large number of British women (mostly of the professional classes) volunteered to mail record cards, month by month, showing the onset date of each mensis. The collection of data continued for one year. A total of 479 women provided information that can be considered reasonably reliable and 291 others furnished less complete data. The typical difference between the shortest and longest cycle is considered to be eight or nine days; in 30 per cent of the women it was over 13 days; in no case was it less than two to three days. The authors conclude: ''The very regular case is either an absolute myth, or it is so rare as to be a medical curiosity.''

The details which have been extracted and computed from these several investigations are presented in Tables IV, V, and VI. It should be noted that many of the items listed do not exist in the original pub-

TABLE V. DETAILED DATA PERTAINING TO MORE THAN 13,500 MENSTRUAL CYCLES FURNISHED BY 973 WOMEN AND GIRLS. THE RECORD OF EACH INDIVIDUAL IN A GROUP WAS FIRST TREATED SEPARATELY FOR MODE, MEAN AND DEVIATIONS AND THEN THESE WERE AVERAGED TO GIVE MEAN VALUES FOR THE GROUP AS A WHOLE

SOURCE OF DATA	MODAL CYCLE LENGTH (DAYS)	MEAN CYCLE LENGTH (DAYS)	MEAN AVERAGE DEVIATION OF CYCLES FROM MEAN (DAYS)	MEAN STANDARD DEVIATION OF CYCLES FROM MEAN (DAYS)	PROBABLE ERROR OF STANDARD DEVIATION (DAYS)	CO-EFFICIENT OF VARIATION	PROBABLE ERROR OF CO-EFFICIENT OF VARIATION
1. Issmer, 1889	28	27.8	2.11	2.56	0.35	9.49	1.31
2. Latz and Reiner, 1935	27; 28	30.8	1.42	1.79	0.08	5.81	0.27
3. Latz and Reiner, 1937	27	27.7	1.39	1.83	0.09	6.53	0.31
4. King, 1933	27	28.9	2.64	3.35	0.35	11.59	1.25
5. Gunn, et al., 1937	26	28.5*	----	4.09	0.09	14.10	0.30
6. King, 1926; 1933	27	28.4	2.04	2.59	0.21	8.98	0.75
7. Scipiades, 1935	29	29.9	----	----	----	----	----
8. Fluhmann, 1934	27; 29	32.4	5.06	6.50	0.35	20.03	1.08
9. Engle and Shelesnyak, 1934	29	33.6	----	14.28	0.68	42.50	2.03
1-8. Means for adults	27	29.3	2.44	3.24	0.22	10.93	0.75
9. Means for pubertal girls	29	33.6	----	14.28	0.68	42.50	2.03

*To make this average comparable with other means in the table, the value of 29.0 days, given by Gunn and his co-workers, has been reduced by 0.5 day. See footnote to Table II for the reason for doing this.

lications except as they lie concealed in the raw data. The grand means at the foot of all tables represent the averages of the individual items; these are simple means designed to show the average values of the several lots of data and intentionally do not attempt to weigh the uneven populations of the component groups. It seems unnecessary to comment specifically on the facts brought out by these tables. For the most part the meanings are clear. In any event, the significance of any portions that may not be apparent at first inspection should become intelligible after the appended section on statistical interpretation (p. 28) has been consulted. It is obvious that in comparing the corresponding data for different groups in Tables IV to VI one must also keep in mind the general, but pertinent, information contained in Table III.

TABLE VI. DATA ON THE DISTRIBUTION OF MENSTRUAL CYCLES WITH RESPECT TO GROUP MEANS AND INDIVIDUAL MEANS. THE TABULATION INVOLVES 8,812 CYCLES FURNISHED BY 644 WOMEN AND GIRLS

SOURCE OF DATA	OCCURRENCE OF CYCLES EQUALLING GROUP MEAN IN LENGTH %	OCCURRENCE OF CYCLES LONGER THAN GROUP MEAN %	OCCURRENCE OF CYCLES SHORTER THAN GROUP MEAN %	INDIVIDUALS NEVER EXPERIENCING OWN MEAN (% OF GROUP)	INDIVIDUALS EXPERIENCING OWN MEAN IN AT LEAST ONE-THIRD OF ALL CYCLES (% OF GROUP)	LOWEST MAXIMUM AND HIGHEST DEPARTURE FROM ANY INDIVIDUAL MEAN (DAYS)
1. Foster, 1889	11.9	59.2	28.9	----	----	----
2. Issmer, 1889	18.3	41.7	40.0	25.0	8.3	2; 12
3. Latz and Reiner, 1935	18.2	40.5	41.3	4.9	35.3	1; 22
4. Latz and Reiner, 1937	16.3	48.9	34.8	4.0	38.0	1; 53
5. King, 1933	9.3	50.9	39.8	33.3	23.8	1; 26
6. King, 1926; 1933	13.5	31.9	54.6	15.2	9.0	2; 20
7. Scipiades, 1935	9.1	52.8	38.1	76.0	5.0	----
8. Pratt, et al., 1929	12.4	39.5	48.1	----	----	----
9. Allen, 1933	11.0	47.5	41.5	----	----	----
10. Fluhmann, 1934	7.5	33.4	59.1	32.9	13.2	2; 69
11. Engle and Shelesnyak, 1934	2.7	11.6	85.7	33.0	1.0	6; 211
1-10. Means, etc., for adults	12.8	44.6	42.6	27.3	18.9	1; 69
11. Means, etc., for pubertal girls	2.7	11.6	85.7	33.0	1.0	6; 211

No previous writer has established clearly the degree of variability exhibited by different age groups. Only Gunn, Jenkin and Gunn (1937) have presented information on this topic. Yet the results of these investigators do not inspire confidence since they show the lowest variability among the young (13 to 22 years; standard deviation, ±2.01 days) and the highest variability at 23 to 27 years (standard deviation, ±7.01 days). But these conclusions with respect to young individuals are directly contrary to general experience. Especially are they at variance with the detailed study on pubertal girls conducted by Engle and Shelesnyak

(1934) who found the standard deviation for the first 22 cycles (mean terminal age, 15.5 years) to be ±20 days and for the first 45 cycles (mean terminal age, 16.4 years) to be ±10 days. However, the two sets of studies are not directly comparable since Gunn had access to only three records in the 13- to 17-year period.

In order to arrive at some firmer conclusion on the relation of variability to age, all the available data used in the present report were sorted into age groups and analyzed. In the furtherance of this Shelesnyak kindly supplied his original records on pubertal girls. It was desired to obtain information on the early, middle, and later periods of adolescence and on the definitely adult woman. Practically all the studies hereto-

TABLE VII. THE DEGREE OF MENSTRUAL VARIABILITY IN RELATION TO AGE. THE MEAN STANDARD DEVIATIONS IN EACH GROUP REPRESENT THE AVERAGE OF INDIVIDUAL MEANS

SOURCE OF DATA	NO. OF SUBJECTS	AGE RANGE OR CYCLE NO. SINCE MENARCHE (ALL INC.)	MEAN AGE OF SUBJECT	MEAN NO. OF CYCLES PER PERSON	MEAN STANDARD DEVIATION FROM MEAN (DAYS)	
Engle and Shelesnyak (1934)	26	1-22nd cycle	14.5*	22.0	20.0	
Engle and Shelesnyak (1934)	18	25-39th cycle	15.5†	15.0	10.36	
Fluhmann (1934)	21	18-19 yr.	ca. 18.5	10.3	5.48	mean, 4.35
King (1926; 1933)	14	18-19 yr.	ca. 18.5	8.9	3.22	
Fluhmann (1934)	15‡	22-27 yr.	23.1	10.4	2.67	mean, 2.27
King (1926; 1933)	33	22-35 yr.	26.6	18.4	2.24	
Issmer (1889)	10	22-39 yr.	28.1	10.0	2.37	
Latz and Reiner (1935; 1937)	200	22-49 yr.	31.4	12.2	1.81	
Gunn, et al. (1937)	336§	23-51 yr.	30.3	13.0	4.57	
Gunn, et al. (1937)	146‖	23-51 yr.	30.7	13.0	3.95	

*Age at the end of the eleventh cycle.

†Age at the end of the thirty-second cycle.

‡One very irregular record of only four cycles (standard deviation, ±35.34 days) was omitted.

§This constitutes Gunn's full group of reasonably reliable cases.

‖A selected group, with most relliable data, chosen by Gunn from the larger group of 336.

fore have been based on mixed groups of young and adult women (Table III), so that the conclusions given in Tables V and VI do not fulfill the present need. The results of these new calculations on the relation of variability to age are summarized in Table VII where decreasing variability with increasing age is shown clearly. Since Gunn's data are not in agreement with the general findings presented in this table, his figures have not been used in obtaining an average value for adults. If his larger value (±4.57 days) is included, then the mean standard deviation rises from ±2.27 to ±2.79 days; including his smaller select group, the average becomes ±2.61 days. It may be concluded that

two out of three menstrual cycles of the average adult woman may be expected to keep within a range of about 2.5 days above and below her individual mean.

Collateral evidence as to the general correctness of the fundamental conclusions concerning the existence of considerable variability in the human menstrual cycle comes from Hartman's (1932) close observations on his monkey colony; there, also, irregularity is the rule. For example, in 392 cycles from 22 selected females the distribution range extended from 14 to 42 days, with the mean set between 27 and 28 days and the mode at 28 days. As in the human being, the wide distribution of cycle lengths is due to the irregularity of each individual and not to differences between regular individuals. The average cycle length for different individuals ranged from 24.6 to 31 days; yet the irregularity exhibited in the detailed menstrual record of almost every animal was marked. Essentially similar evidence is to be found in the recent study of Elder and Yerkes (1936) on the sexual cycle of the chimpanzee. For 164 cycles of 11 presumably normal and mature animals the cycle length varied between 29 and 53 days; the average for all cycles was 36 days, the mode 35 days. The smallest difference between the shortest and longest cycle of any animal was 9 days; the largest difference was 23 days. Like the human female, both of these primates are not at all regular, and with the newer understanding of the factors governing menstruation one could scarcely expect it to be a wholly perfect mechanism, either in monkey or in man.

SUMMARY AND CONCLUSIONS

1. Only the records of consecutive menses, set down at the time of occurrence, are of value in studying the duration and variability of menstrual phenomena. Ordinary hospital histories, oral testimony, and similar data which depend on unaided memory cannot be given serious consideration since experience proves them to be utterly unreliable.

2. Some 20,000 calendar records from about 1,500 women and girls, as given in 12 different studies, have been assembled, corrected and analyzed.

3. The commonest length of 8,462 cycles (furnished by 585 persons) considered as a unit, is 28 days both for pubertal girls and adult women. The average length of all cycles is 33.9 days for girls and 28.4 days for women.

4. The commonest length of 17,652 cycles (the grand mode of the individual modes of 1,265 persons) is divided between 30 and 31 days for pubertal girls and is 27 days for adult women. The mean length of cycle, based on individual averages, is 33.6 days for girls and 29.5 days for women.

5. Statements concerning grand means and modes, however, have little significance in pubertal girls since they are so unrepresentative of the wide variability encountered.

6. The maximum departures of individuals from their means extends from 1 to 69 days in adults and from 6 to 211 days in pubertal girls.

7. The smooth frequency distribution, obtained from combining all the cycles of a group into one curve, is the result of overlapping individual irregularities and not of closely spaced, regular, individual performances.

8. The existence of favored, subordinate types of cycle length (such as 3, 5, 6 and 7 weeks), in addition to the modal type, do not appear either in the massed cycles of groups or in the records of individual performance. This is in sharp contrast to the conclusions based upon oral testimony.

9. In the first few years of the menstrual function the cycle length is extremely variable (7 to 256 days). It can be calculated that during the period of observation employed (averaging 31 cycles per person) one-third of the 100 pubertal girls never had a cycle that corresponded with their own means. Only one girl experienced her own mean as often as once in three cycles. From menarche to the twenty or twenty-fourth cycle, only two-thirds of the total cycles of an average individual kept within a 20-day range above and below her mean. Yet in middle adolescence, occupied by cycles 25 to 39, the regularity improved to such an extent that, on the average, two-thirds of all the cycles kept within a 10-day range.

10. At the end of adolescence, during the eighteenth and nineteenth years, the variability is still further reduced. In the 35 individuals studied, two-thirds of the cycles kept within a range of ±4.4 days with respect to the mean.

11. In several hundred adults more than 21 years old, a fluctuation of about ±2.5 days with respect to the mean expresses the limits of variability which contain two-thirds of all cycles. Expressed differently, an average adult woman must expect one-third of all her cycles to depart more than two days from her mean cycle length.

12. The amount of variability shown by adults is greater than ordinarily is credited. Cycles ranging from 2 or 3 weeks to 7 or more weeks appear in all of the groups (17 to 49 years) from which data have been collected. In the records of more than 500 women, 27 per cent never showed their own means during the observation period which averaged 11 cycles in length. Only 20 per cent experienced their own mean in at least one-third of their recorded cycles.

13. The adults, reported in detail by 11 different investigators, represent all ages from late adolescence to approaching menopause. They include American, Canadian, British, German, and Hungarian subjects, and they sample various grades of society. In no instance did an example of perfect menstrual regularity appear over any significant period of time; this is all the more noteworthy since many individuals had previously declared themselves to be the acme of invariability. The most regular records are short ones. In a separate (unpublished) study of menstrual records extending as long as 20 years, it will be shown that temporary successions of atypical regularity (or irregularity) may occasionally interpose themselves in a rhythm of fundamentally different characteristics. It is these unrepresentative fragments of the true record that sometimes lead to erroneous conclusions concerning an individual rhythm; even a record extending for over a year may prove to be unrepresentative.

14. In the face of all these facts it seems improbably that menstrual regularity, in any true sense of the word, ever will be encountered over

significant periods of time. Certainly, not the slightest evidence pointing toward perfect regularity has so far been produced for even a single exceptional individual. Should such a person be found at some future time, she will constitute a true medical curiosity.

15. Studies on the monkey and chimpanzee disclose menstrual irregularity comparable to that of the human being.

STATISTICAL METHODS USED AND THEIR INTERPRETATIONS

Data can be interpreted properly only through the use of proper statistical methods. Since many are unfamiliar with these methods, and especially with the interpretations to be made from such numerical findings, it seems desirable to explain the procedures used in the present study.

A. *Measures of the Central Tendency:*

1. The arithmetic mean (M) is the sum (Σ) of the separate variates (v) divided by the number of variates (N).

$$M = \frac{\Sigma\ v}{N}$$

2. The *mode* is the class with the greatest frequency.

B. *Measures of Variability:*

1. The *range* is the total spread of distribution from the lowest to the highest. It tells nothing about the shape of the distribution or the degree of concentration about the central tendency.

2. The *average deviation* (AD) is the average of the individual deviations from the mean (regardless of sign).

The individual departure of each variate from the mean (v - M) is found by subtraction. The sum of these is next obtained without regard to whether a deviation lies above or below the mean. Finally, this sum (Σ) is divided by the number of variates (N).

$$AD = \frac{\Sigma\ (v - M)}{N}$$

The average deviation of a normal distribution marks the limits of the middle 57.5 per cent of the measures. Applied to the present study, the chances are slightly better than even that the length of a random menstrual cycle will lie within the limits of the average deviation from the mean.

3. The *stand deviation* (σ) is the square root of the mean of the squares of the deviations from the mean.

To find this value, each individual variation from the mean is squared $(v - M)^2$; these are then summated (regardless of sign) and divided by the number of variates (N). Finally the square root of this mean value is extracted.

$$\sigma = \sqrt{\frac{\Sigma\ (v - M)^2}{N}}$$

The standard deviation of a normal distribution marks the limits of the middle 67 per cent of the measures. Applied to the present study, it may be expected that two cycles out of three will lie within the limits bounded by the standard deviation. Similarly, a variation equal to twice and thrice the standard deviation can be expected only once out of 22 and 370 cycles, respectively.

4. The *coefficient of variation* (CV) is a value obtained by reducing a standard deviation to an abstract number which then allows this particular standard deviation to be compared directly with any other standard deviation similarly treated. It is obtained by multiplying the standard deviation by 100 and dividing by the mean. Hence it expresses relative variability in terms of per cent of the mean.

$$CV = \frac{100\ \sigma}{M}$$

C. *Measures of Probability.*—

The *probable error* (PE) gives the measure of unreliability of any determination. It is a pair of values, one lying above and the other below the determination being

tested. The chances are even that the true value lies within the range of the probable error. The chances that the true value lies within ±2 PE are 4.6:1; similarly the chances that the true value lies within ±3 PE are 22:1.

1. The *probable error of the standard deviation* is obtained by multiplying the standard deviation by 0.67 and dividing by the square root of twice the number of variates.

$$PE_{\sigma} = \pm \frac{0.67\ \sigma}{\sqrt{2N}}$$

2. The *probable error of the coefficient of variation* is obtained by multiplying the coefficient of variation by 0.67 and dividing by the square root of twice the number of variates.

$$PE_{cv} = \frac{0.67\ CV}{\sqrt{2N}}$$

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Sasaki, S.: On the Effect of the Function of the Anterior Pituitary Lobe on Narcosis, Jap. J. Obst. & Gynec. **20**: 620-632, Nov., 1937.

The author studied rabbits which were subjected to general anesthesia by means of chloroform. He injected one group with anterior pituitary gonadotropic hormones and found that the duration of anesthesia was decreased but the recovery time showed no change. The effects of the injection of anterior pituitary hormone were almost identical with those produced by estrin. When the pituitary gland was irradiated with large doses of roentgen rays the duration of the anesthesia was increased and the recovery time decreased. Prominent regressive degeneration was observed in the pituitary gland and in the ovaries after strong irradiation of the pituitary gland with x-ray.

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RETINAL EXAMINATIONS

A Guide in the Management of the Toxic Hypertensive Syndrome of Pregnancy*

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APPROXIMATELY 10 per cent of pregnant women throughout this country exhibit some evidence of late toxemia of pregnancy, such as hypertension, albuminuria, and edema. Stander[13] and Peckham[9-11] independently arrived at this figure, and Peckham stated that this incidence was 17 per cent or greater among the pregnant women admitted to the maternity service at Johns Hopkins Hospital. Reports from various observers indicate that the percentage of women who have toxemia varies with the locality and living conditions. However, every physician attending a pregnant woman must be alert to detect symptoms of late toxemia of pregnancy and to undertake the management of various phases of this condition.

It has become increasingly evident that various conditions which formerly were grouped under the term, "albuminuria" of pregnancy, can be divided into those which were present prior to the pregnancy they complicate and those which arise in the course of pregnancy. It has been shown that chronic arterial disease and chronic nephritis (chronic glomerulosclerosis) antedating pregnancy are associated with pathologic findings and clinical syndromes which differ in many respects from those of late acute hypertensive toxemia which develops during pregnancy. For purposes of clarity in this paper, I shall use the terms "chronic arterial disease" or "chronic renal disease" to define antecedent conditions of this nature and "hypertensive" or "late toxemia of pregnancy" to define the acute late toxemia of pregnancy; the latter is subdivided into nonconvulsive, mild and severe toxemia (pre-eclampsia), and convulsive toxemia (eclampsia).

The majority of writers, in recent years, are agreed that pathologic and clinical findings in cases of acute late toxemia of pregnancy show evidence of more or less generalized vascular disease, primarily a condition of arteriolar spasm throughout the body. Acosta-Sison and others have presented evidence that vascular damage is the basis of the pathologic changes in the liver, kidneys, brain, and heart. Likewise, examination of patients suffering from severe nonconvulsive toxemia (pre-eclampsia) and convulsive toxemia (eclampsia) usually demonstrates the presence of spasm of the small arteries of the retina and of

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Ophthalmoscopic examinations were performed by consultants of the Section on Ophthalmology.

the capillaries of the nail fold. Furthermore, in most instances, accurate retinal examination will reveal a distinct difference between the retinal changes produced by chronic vascular sclerosis or chronic nephritis and those present in cases of acute late toxemia of pregnancy. Cheney,[3] Wagener,[14] Hallum,[4, 5] and others reported that changes often occurred in previously normal retinal vessels in the course of late toxemia of pregnancy. Wagener made the important observation that acute vascular changes in the retina were sometimes superimposed on lesions characteristic of chronic vascular disease.

Addis accepted the hypothesis that arterial spasm is a frequent pathogenic factor underlying and uniting the various symptoms of late toxemia. He explained that the effects produced by angiospasm in the various organs may appear to be completely unrelated: in the brain, resulting in hypertensive encephalopathy; in the kidney, disturbance of function (glomerular vascular damage); in the liver, periportal thrombosis; in the subcutaneous tissue, anasarca. He suggested that these manifestations are the result not of varying causes but of the kind of tissue on which the single cause acts, and that vascular spasm is the factor which underlies and unites all the manifestations of pre-eclampsia and eclampsia.

Addis, Herrick, Irving, and others appear to be correct in emphasizing the role of vascular spasm in the production of the syndrome of toxemia, although the cause or causes responsible for the angiospasm have not been proved. Herrick stated that differences between the mild and more severe types of late toxemia are of degree, not of kind, and that the role of the kidney is not fundamental but is dependent on the vascular structure of its glomerular tufts and its copious blood supply as an excretory organ. If it is assumed, then, that in both the nonconvulsive and convulsive forms of the acute hypertensive toxemia of pregnancy, there is an underlying general systemic vascular spasm, we are prepared to accept hypertension as the important and outstanding symptom of this disease. Evidence strongly supports the supposition that hypertension is the result of generalized arterial spasm of undetermined cause and that the appearance of hypertension is preceded by functional spasticity of the glomerular, retinal, and other arterioles which, perhaps, would not be recognized in its incipiency.

In a broad sense, the degree of severity of acute hypertensive toxemia is measured more by the height of blood pressure than by any other symptom or finding. Also, permanent vascular and glomerular damage which may follow acute toxemia seem to depend on the height of the blood pressure and the length of time the hypertension, or the toxin producing it, is imposed on the vascular system. Follow-up studies, notably by Peckham, Herrick, and others have shown that chronic cardiovascular disease or chronic glomerular sclerosis occurs among many women as a direct consequence of acute hypertensive toxemia. According to Peckham and Stout, repeated examinations of patients whose condition was diagnosed as low reserve kidney (considered by many to be mild late toxemia of pregnancy) revealed that, five years later, approximately one-half of these patients had evidence of chronic arterial disease or chronic nephritis. This incidence rises with the height and duration of the hypertension, the condition being notably frequent among those whose systolic pressure registered more than 200 mm. of mercury.

Discussion of the management of acute hypertensive toxemia must include, also, consideration of chronic cardiovascular disease and chronic nephritis which antedate pregnancy. When definite chronic nephritis

or extreme hypertension is susceptible of diagnosis early in pregnancy, management of such a case often differs sharply from that of acute hypertensive toxemia, the symptoms of which appear later in pregnancy. Detailed descriptions of differential diagnosis and tests for renal function are not germane to the subject of this paper. However, inspection of the retina deserves mention, because evidence of chronic retinal arterial changes or nephritic retinitis may be demonstrable even when the results of tests of renal function are not diagnostic. If pregnancy is complicated by pre-existing chronic vascular sclerosis or chronic nephritis, there is a marked tendency toward exacerbation of the pre-existing disease in the first or early in the second trimester, and continuation of pregnancy usually results in a much more serious condition than before. Sometimes, patients who have so-called occult nephritis, which may not be susceptible of definite diagnosis prior to pregnancy and some who have mild hypertension may pass through pregnancy without superimposed toxemia.

I have reviewed the pathogenesis of conditions classified as late toxemia of pregnancy, because the concept that more or less prolonged acute, general, vascular spasm is responsible for permanent cardiovascular and glomerular injury, which may follow toxemia of pregnancy, has emphasized the need for the termination of pregnancy in certain of these conditions. In addition to readings of the blood pressure, results of examinations of the urine, evaluation of subjective symptoms and, occasionally, chemical examinations of the blood, a valuable index of the degree of spasm of the vascular system and the rate at which this spasm is progressing, is furnished by changes observed in the vessels of the retina. In a previous paper I noted that, in the course of routine ophthalmoscopic examination of pregnant women, Masters found that, in every case in which the blood pressure was elevated to 150 mm. of mercury or more, there was narrowing of the caliber of the retinal arteries. Among 44 cases of toxemia, he observed this retinal change in 3 cases in which the blood pressure was initially less than 150 mm. of mercury but subsequently rose much higher. Wagener found there were retinal changes in 70 per cent of pregnant women whom he examined, and whose systolic blood pressure was more than 140 mm. of mercury. Later Hallum quoted similar findings.[4]

Wagener also states: "In cases of toxemia of pregnancy in which there is an associated rise in blood pressure, changes in the arterioles appear first and those in the retina proper, commonly called 'retinitis' are secondary to and apparently dependent on, the changes in the arterioles. The caliber of the arterioles appears narrowed and the lumen is reduced because of spastic contraction and increased tonus of the walls of the arterioles. This change in the arterioles may disappear entirely if there is early and permanent fall in blood pressure. The constriction soon becomes fixed if the toxemia progresses. When the constriction of any arteriole becomes so fixed and severe as to cause secondary capillary ischemia or stasis, localized edema and hemorrhage appear in the adjacent retina. If the toxemia continues, this spastic constriction may become so generalized and severe as to produce diffuse retinitis of the albuminuric type, the classic 'retinitis of pregnancy nephritis.' The presence or absence, or the advancement of the involvement of the arterioles can be determined best by frequent systematic examination of the retina."

It was found that Wagener's description of the retinal changes in cases of acute toxemia of pregnancy could be divided into four stages or grades, related to the severity and duration of the hypertension: Grade 1, the first sign of which is spastic narrowing of the arterioles of the retina, which may affect all branches of the central artery; Grade 2, in which irregular constriction of the lumens of the arterioles usually appears first or to a more severe degree in smaller nasal branches, sometimes varying in situation or degree from day to day; Grade 3, in which narrowing and constriction are more fixed and individual cotton-wool patches and hemorrhagic regions may appear in the retina; and Grade 4, in which diffuse retinitis of the albuminuric type is found. By the use of this system of grading of progressively severe retinal changes, a tabulation, previously reported, was made of the retinal examinations of 108 patients who had late toxemia of pregnancy; in 14 of these cases, there was pre-existing hypertension. The data indicated that (1) all patients who had a systolic blood pressure of 200 mm. of mercury or higher had evidence of acute retinal changes, most of them severe, (2) 90 per cent of the patients who had a systolic blood pressure between 170 and 200 mm. of mercury had retinal changes, and (3) only 52 per cent of those whose systolic pressure was less than 160 mm. of mercury had retinal changes, which were predominantly mild in character. It was shown also that there was a progressive relationship between the higher systolic blood pressure and more severe changes in the retinal arterioles. Comment was made that, in a number of cases, the retinal arteriolar changes were the deciding factors in determining if, and when pregnancy should be terminated. Hallum recently stated: "The obstetrician will find that a study of the eye grounds, when considered with the other signs of toxemia, will be a real aid, probably the most consistently reliable single guide in determining when pregnancy should be terminated."

As this paper is concerned with the influence of retinal examinations on the management of late toxemia of pregnancy, other phases of treatment will not be considered in detail. In brief, the objects of treatment are, first, to reduce the incidence of late toxemia and eclampsia, second, to prevent mild toxemia from becoming severe, third, to effect improvement in toxemia which has become severe, and fourth, to shorten the course of the disease. Shortening the duration of toxemia by spontaneous or artificial termination of pregnancy usually is followed by relief of symptoms and cessation of the toxemia. When symptoms of toxemia are detected early, the institution of appropriate measures may avert progression. In spite of treatment, mild symptoms may become severe or the patient may be observed for the first time with symptoms of severe toxemia. Her condition may approach so nearly the eclamptic state that measures to avert convulsions must be carried out urgently. Sedation, dietary restriction, limitation of fluids, careful use of solutions of glucose or magnesium sulfate, or both, will be followed usually by somewhat lowered blood pressure, increased output of urine and lessened edema. When toxemia is severe and when the patient fails to improve, or when, following improvement, there is a relapse, termination of preg-

nancy is indicated in the interest of the mother. However, gestation may have reached so nearly the time at which there is a reasonable chance for the fetus to survive, that delay in the interest of the fetus is most desirable.

The probability of survival among babies born of women suffering from toxemia is less than normal and this is especially the case when the babies are premature. The fetus may die in utero, if overwhelmed by maternal toxin during the course of severe toxemia. Also, as previously stated, the number of women who have chronic arterial disease and chronic nephritis as a consequence of late toxemia of pregnancy, increases proportionately to the height of the blood pressure and duration of the toxemia. A nicety of judgment may be required in deciding whether pregnancy should be terminated and in selecting the proper time and method of interruption.

The method of terminating pregnancy depends on a number of factors, including age, parity and condition of the patient, duration of pregnancy, adequacy of the bony passage, and condition of the cervix.

For reasons previously stated, in the interest of both mother and fetus, the optimal time for terminating pregnancy must be selected carefully. This decision must rest chiefly on the period of gestation and the duration and severity of the toxemia. Evaluation of the severity of the toxemia depends mainly on subjective symptoms of headache, visual disturbance, epigastric pain and such clinical findings as hypertension, albuminuria, and edema. The reliability of chemical examinations of the blood to determine the severity and progress of such toxemia is debatable. When the toxemia is comparatively mild and when the systolic pressure is less than 150 or 160 mm. of mercury, the necessity of terminating pregnancy arises rarely; when the patient is in the most severe nonconvulsive stage and has a blood pressure of about 180 mm. of mercury or more, induction usually is indicated; when the patient is in the moderately severe stage and has a systolic blood pressure of 160 to 180 mm. of mercury, the problem if and when labor should be induced may be most perplexing. In nearly all such cases, examinations of the retina will reveal changes in the retinal arteries. Those skilled in the use of the ophthalmoscope usually can determine whether these changes are a residuum of pre-existing arterial or glomerular disease, whether they are characteristic of acute toxemia, or whether the acute changes are superimposed on old arterial sclerosis. Repeated examinations determine whether acute vascular changes are advancing, receding, or stationary.

For the past fifteen years, information obtained from examination of the retina has been increasingly useful to us in the management of late toxemia. This information often has influenced the obstetrician to decide for or against termination of pregnancy. For example, interruption of pregnancy has been undertaken when retinal examination gives evidence of advance in the vascular lesion, although there has been no untoward change, or, perhaps, apparent improvement has occurred in the patient's clinical condition. Induction of labor on this additional evi-

dence, we believe, has averted an increase in severity of toxemia in a number of cases. In other cases, interference has been avoided when retinal examination has revealed either a normal retina or, on repeated examination, no advance of the acute vascular spasm, or perhaps evidence only of previous arterial changes. Such evidence often has permitted further observation and delay, thereby increasing the chances of survival of the fetus without needlessly jeopardizing the mother.

Retinal examination prior to delivery was recorded in this series of 167 patients who had hypertension and other symptoms of late toxemia of pregnancy. Examination of 117 of these patients revealed varying degrees of arterial spasm characteristic of acute toxemia, 23 had evidence only of chronic vascular sclerotic change characteristic of pre-existing cardiovascular disease, and 27 gave no demonstrable evidence of a retinal lesion. Nearly all of the last group had comparatively mild toxemia. Including those patients with chronic changes, 83 per cent on examination gave evidence of retinal involvement. The percentage of cases in which there was evidence of changes in the retina increased directly with the height of the blood pressure. The incidence of patients whose retinas had undergone changes, with the corresponding blood pressures is as follows: 51 per cent, never more than 150 mm. of mercury, 84 per cent, between 150 and 169 mm., 92 per cent, between 170 and 199 mm., and 100 per cent, 200 mm. or more.

Although the presence of retinal changes was of diagnostic value in 140 cases or 83 per cent of the entire series, it is not our intention to imply that the degree of vascular spasm was the sole determining factor on which the decision of whether or not to interrupt pregnancy was based. Among the more severe cases of toxemia and among cases of eclampsia, the symptoms and condition of the patient frequently indicate the need for termination of pregnancy. However, there are many cases of late toxemia in which a drop in blood pressure and lessened edema occur following rest, sedatives, and diuresis. The blood pressure may not be alarmingly high and the patient may not feel particularly ill. In such cases, frequent, sometimes daily, examinations of the retina may reveal progressive changes, which presage a similar advance of generalized arteriolar involvement before the appearance of a further rise in blood pressure or other significant symptoms. In 51, or 43.5 per cent, of the 117 cases, evidence of a progressive increase in retinal arteriolar spasm was an influencing and, frequently, a deciding factor in the decision to terminate pregnancy. Spontaneous onset of labor decided the problem in many additional instances. Among 22, or over 18 per cent, of the cases, the retinal changes were stationary or had regressed. These findings directly influenced the decision that the safety of the patient was not jeopardized unduly by deferring interruption of pregnancy in the interest of the fetus. Also, among a group of some 12 patients whose systolic pressures ranged from 150 to 200 mm. of mercury, the absence of any evidence of vascular change undoubtedly influenced the decision not to terminate pregnancy. Among some of the 23 patients who had pre-existing hypertension, many of whom were not

seen early in pregnancy, the differential diagnosis between chronic arterial disease and acute toxemia was made possible by retinal examination which revealed chronic rather than acute vascular lesions.

In this series of cases of late toxemia of pregnancy, the first examination of the retina was recorded in 1922. Since that time the Section on Ophthalmology at the Mayo Clinic has cooperated fully in carrying out these examinations. The presence and degree of spasm of the retinal arteries has paralleled so closely clinical evidence of the severity of toxemia that we have increasingly depended on this examination. Dividing these fifteen years into three five-year periods, it is noteworthy that retinal examination has been a distinct guide to the management of late toxemia of pregnancy in approximately 28 per cent of the cases in the first five-year period, in 51 per cent in the second five-year period, and in 56 per cent in the last five years.

COMMENT

The weight of evidence indicates that acute late toxemia of pregnancy presents a hypertensive syndrome which is characterized by generalized spasm of the smaller arteries. The degree of systemic vascular spasm appears to parallel the height and duration of the blood pressure and the severity of the toxemia. Examination of the arterioles of the retina reveals changes which apparently manifest the degree of angiospasm throughout the body. In addition to hypertension and other symptoms, the presence and persistence of noticeable retinal vascular spasm is a guide in the management of late toxemia. This finding often indicates the need of avoiding further generalized and, perhaps, permanent vascular damage by using measures to terminate pregnancy when the condition of the patient permits. On the contrary, the presence of retinal changes of comparatively mild degree, or the absence of such changes, may indicate that pregnancy may be allowed to continue in the hope of obtaining a living infant without unduly jeopardizing the safety of the mother.

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URIC ACID METABOLISM IN ECLAMPSIA

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IT IS well established that eclampsia is accompanied by a definite elevation in blood uric acid,[11, 19] although the concentration of the other known nitrogenous elements may remain within normal limits. The significance of this observation is as yet not known, not even so far as it may or may not be associated with the etiology of this disease, about which we are still ignorant.

In birds and reptiles nitrogenous waste products are excreted chiefly in the form of uric acid, a process probably associated with an adaptation to urgent need of water preservation in arid regions. In mammals, on the other hand, these end-products of nitrogen metabolism are chiefly excreted in the form of urea, which, apart from water, is the main constituent of human urine.

In man the formation of uric acid is chiefly from nucleoproteins, exogenously from the purines in the ingested food and endogenously from the nucleoproteins of body cells. In addition, synthesis of uric acid may occur, the nitrogen source being ammonia or amino acids, according to Schuler and Reindel.[9] The carbon source for such synthesis is still unknown. The disintegration of nucleic acid depends upon several steps and enzymes, the final step in man being the oxidation of xanthine to uric acid. Unlike the case in lower animals, in the human uric acid is most probably not destroyed to allantoin unless to an exceedingly small extent. Wiechowski[16] found only 10 to 15 mg. of allantoin per day, as compared with 300 to 500 mg. of uric acid in the urine of man. The source of xanthine oxidase in man, necessary for the formation of uric acid, is in the liver, and thus it has been assumed that uric acid formation takes place wholly in the liver. There may, of course, be other methods of formation, although at present there is no evidence in support of such an assumption. That some uric acid destruction occurs in man is still a controversial problem, although the weight of evidence is in favor of such a conclusion. The end-product of such destruction is unknown, unless it be urea. It is also probable that excessive uric acid may be excreted to some extent into the bowel where disintegration by intestinal bacteria may take place. In dogs uricolysis occurs, and undoubtedly the site of this destruction is the liver as proved by the accumulation of uric acid after liver extirpation experiments by Bollman, Mann and Magath,[2] as well as by the quantitative experiments on allantoin by Schittenhelm and Chrometzka.[8]

The mechanism of uric acid excretion through the kidneys is still not quite clear. Berglund and Frisk[1] conclude that only a small part of the blood uric acid is filtrable, although Homer Smith[10] is of the opinion that uric acid is filtrable from human blood and attributes its failure to be excreted to tubular reabsorption. As normal kidneys concentrate urea about 80 times and uric acid only about 20 times, it has been supposed that uric acid is less easily excreted by the kidneys, especially when diseased, than are the other chief nitrogenous constituents. This assumption, however, is not supported clinically, as uric acid is not the first of the nitrogenous substances to be retained in nephritis. The normal kidney concentration factor, in the case of uric acid, is probably that low because of tubular reabsorption, as suggested by Homer Smith.

Rangier[7] believes that uric acid appears in the urine in the form of a ureide compound together with urochrome, a theory which will explain its great solubility.

Following the discovery of uric acid in 1776 by Sheele, Fourcroy was able to oxidize this substance, by means of chlorine water, to urea. The constitution of the purine group was worked out in great part by Emil Fischer. In 1902 Wiener showed, by means of feeding urea and 3 carbon acids to birds, the metabolic relationship of uric acid to urea and lactic acid. The two isomers of uric acid, formed by shifts of "H" atoms, were named lactim and lactam by Baeyer, and it is probable that in the blood, uric acid occurs as a mixture of these two isomers.

The uric acid content in human blood may be influenced by the amount of purines and also fat in the diet. Harding and his co-workers have shown that diets high in fat, resulting in ketosis, increase the amount of uric acid in the blood. This may be due partly to decreased elimination, resulting from concentration of the blood following high fat diet. Quick[5] has shown that uric acid excretion may be depressed by ketosis, by lactic acid, and aceto-acetic acid, in other words, by substances that reduce the formation of glucuronic acid. Lewis and Karr[4] showed that benzoic acid very definitely decreases the excretion of uric acid. On the other hand, substances which stimulate the production of glucuronic acid, such as pyruvic acid, increase the excretion of uric acid.

It is interesting to note that Quick[6] has recently found that in certain liver ailments, the depressing effect of benzoic acid on the excretion of uric acid is markedly augmented. It should also be pointed out that when nucleoproteins are excessively destroyed, as in leucemia and pneumonia, the uric production is increased.

The amount of uric acid in the blood of man, under normal conditions and a regulated diet, varies between 2.5 and 4.5 mg. per 100 c.c., according to the methods of Folin and Benedict. However, as yet, we do not know exactly how closely the results obtained by these methods approximate the actual amounts in the blood, and, therefore, the standards used in any study are dependent upon the method of analysis employed. The distribution of uric acid between cells and plasma evidently may vary considerably. Theis and Benedict[14] were unable to detect any constancy in the relative distribution.

The amount of uric acid excreted by an adult on a purine-free diet varies between 0.3 and 0.5 gm. per day. Burian and Schur[3] believe that the source of the endogenous uric acid is the oxidation of the hypoxanthine of the muscles, and are of the opinion that the amount excreted represents only about 50 per cent of that formed in the body, from either exogenous or endogenous sources. This question of uric acid destruction in man is, of course, still an unsettled problem. Wells[15] reported a case of bichloride poisoning with almost complete anuria for nine days, where there was no accumulation of blood uric acid, although the tissues contained relatively large amounts of uric acid, while the liver showed only 1 mg. per 100 gm. of tissue. From this observation, as well as from the results of uric acid injection experiments, it seems that a certain amount, 30 per cent or more, of uric acid is normally destroyed and that this probably occurs in the liver.

In order that we may perhaps obtain an understanding of the high blood uric acid values in eclampsia, repeated blood and urine uric acid determinations were performed in five eclamptic patients. In all in-

stances twenty-four-hour urine specimens were collected for the analyses. The periods of chemical study in these women varied from eight to twenty-one days. For the uric acid analyses in the urine we employed the method of Benedict and Hitchcock and for those in the blood, that of Folin.

In Chart 1 are plotted the averages of the findings of the routine chemical analyses of the blood in 132 consecutive eclamptic patients. A study of this chart substantiates the statement, made above, that the blood uric acid in eclampsia is

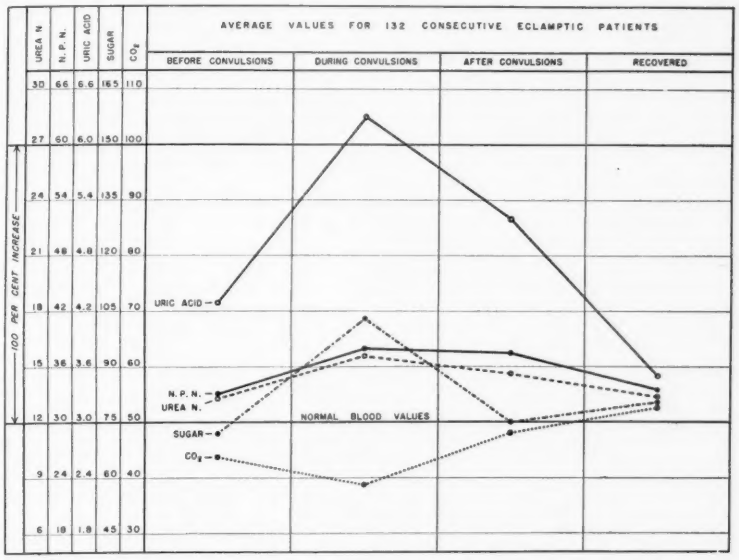

Chart 1.—Average values for 132 consecutive eclamptic patients.

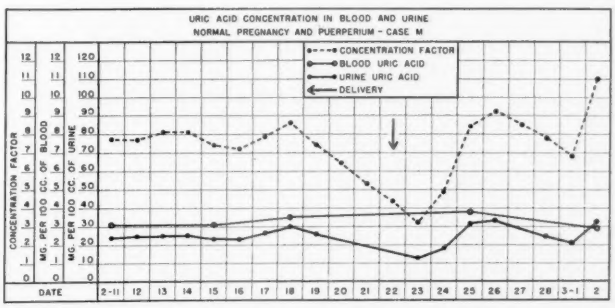

Chart 2.—Uric acid concentrations in blood and urine. Normal pregnancy and puerperal. Case M.

definitely increased, although the concentrations of the urea nitrogen and the non-protein nitrogen show no similar elevation. This increase shows in the early development of the disease is most marked during the period of convulsions and disappears after full recovery.

Chart 2 represents a study of the uric acid concentration in the blood and urine in a control, a normal pregnant woman, over a period of twenty-nine days, covering the last three weeks of gestation, labor, and the first week of the puerperium. The uric acid in the blood and the urine, is plotted in milligrams, per 100 c.c. of blood

and per 100 c.c. of urine, respectively. The curves show the remarkable constancy of uric acid concentration in both blood and urine. A third curve is shown, representing the concentration factor, obtained by dividing the urine concentration by that of the blood. It will be noted that this factor is likewise fairly constant, fluctuating downward only at the time of delivery.

In Charts 3, 4, 5, 6, and 7 are shown the uric acid concentrations in the blood and urine of the 5 eclamptic patients. The concentration factor for uric acid,

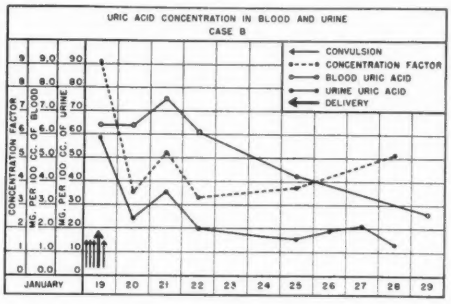

Chart 3.—Uric acid concentrations in blood and urine in ante-partum eclampsia. Case B.

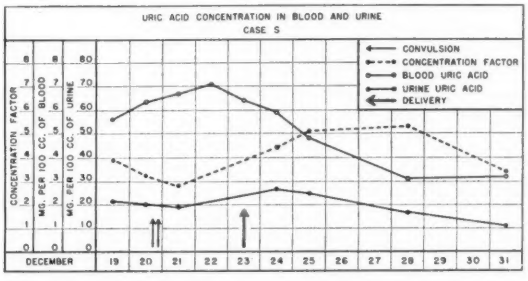

Chart 4.—Uric acid concentrations in blood and urine in ante-partum eclampsia. Case S.

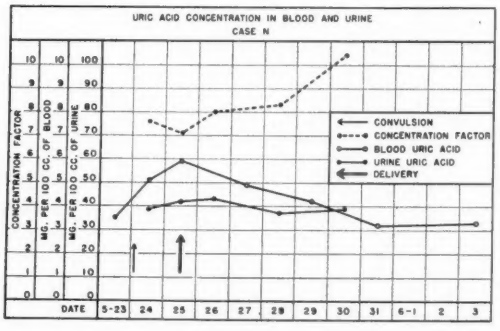

Chart 5.—Uric acid concentrations in blood and urine in ante-partum eclampsia. Case N.

calculated in the manner described above, is plotted for each patient, while the charts also indicate the number and time of convulsion and the time of delivery. In 4 of the patients the eclampsia was of the antepartum type, while in one it occurred in the puerperium (post-partum eclampsia). A study of these 5 charts reveals the high blood uric acid during the convulsive period, the rather constant and

unimpaired uric acid excretion as shown by the concentration in the urine and, lastly, that the uric acid concentration factor is not below the normal limits during the height of the disease. In one case (Chart 3) the concentration factor appears to be highest at the time of convulsions, while in another (Chart 5) it is highest at the time of complete recovery.

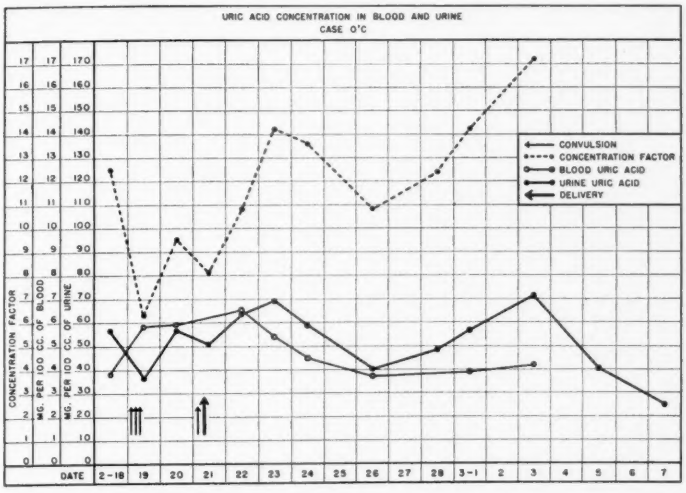

Chart 6.—Uric acid concentrations in blood and urine in ante-partum eclampsia. Case O'C.

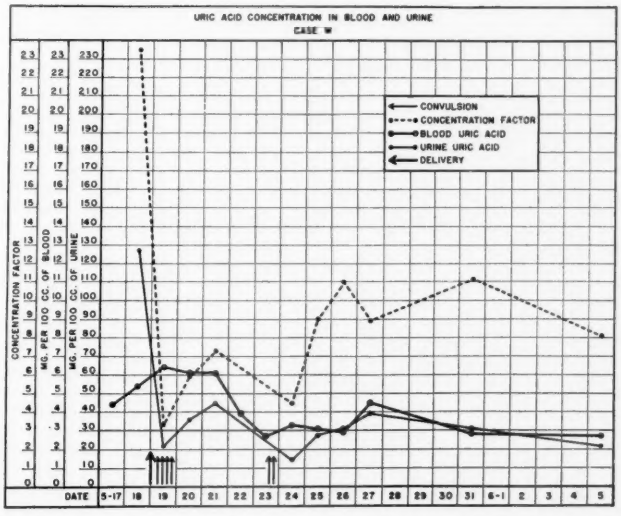

Chart 7.—Uric acid concentrations in blood and urine in post-partum eclampsia. Case W.

A composite chart (Chart 8) has been prepared using the average values in the four cases of antepartum eclampsia at the time of convulsions and delivery, and at daily intervals preceding and following this period of acute involvement. The resulting curves corroborate the interpretations we have placed on the individual charts. It seems a justifiable conclusion that the kidney concentration factor for uric acid is not decreased during the eclamptic seizure and furthermore, is not at a lower

level than at the time of complete recovery, as indicated by the value on the eighth day following delivery. In other words, uric acid excretion does not appear to be impaired, to even a minor extent, in patients suffering from eclampsia.

As we wished to compare the concentration of uric acid in the blood with that in the urine, we have presented, in the above charts, the amount of uric acid in 100 c.c. of urine, although the total amount of

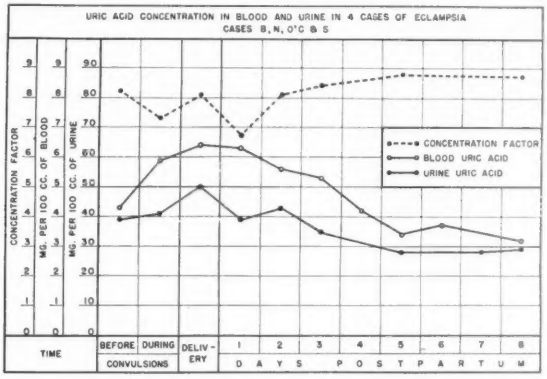

Chart 8.—Uric acid concentrations in blood and urine in four cases of ante-partum eclampsia. Averages.

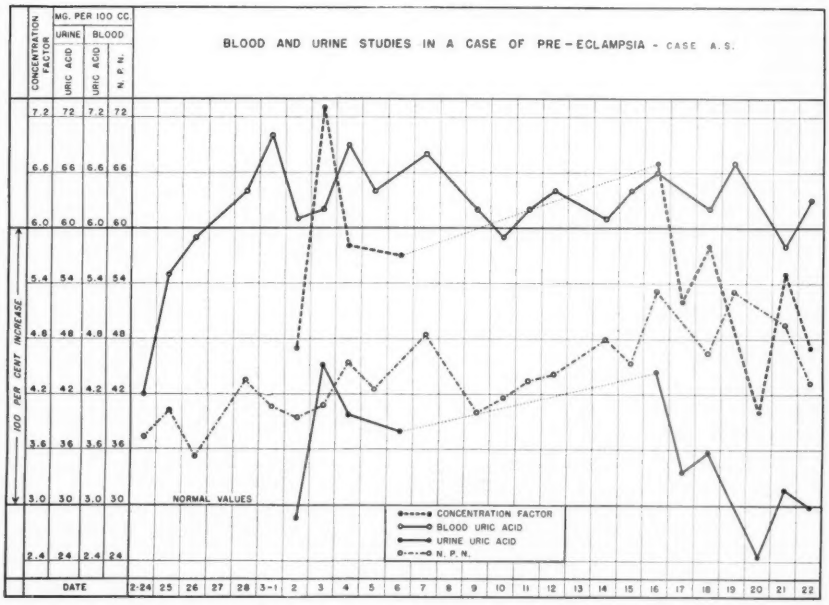

Chart 9.—Uric acid concentrations in blood and urine and nonprotein nitrogen in blood in case of pre-eclampsia.

uric acid excreted in each twenty-four-hour period studied was determined in all instances. These total amounts of uric acid, excreted daily by the five eclamptic patients, are shown in Table I. The individual, as well as the average, amounts excreted are within the normal limits as given in the earlier part of this paper.

TABLE I. TOTAL URIC ACID EXCRETION, EXPRESSED IN GRAMS PER 24 HOURS

CASE		DAYS ANTE-PARTUM PERIOD			DAY OF DELIVERY	DAYS POST PARTUM														
		3RD	2ND	1ST		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
S	Convulsion	2																		
	Uric acid	0.36	0.41			0.56		0.30	0.37	0.46	0.46	0.35	0.37	0.32				0.31		0.29
B	Convulsion				4															
	Uric acid				0.56	0.71	0.47	0.76		0.62	0.64	0.70	0.51	0.34						
O'C	Convulsion		3		1															
	Uric acid	0.39	0.13		0.27	0.95	0.90	0.33		0.46		0.57	0.46		0.28			0.33		
N	Convulsion			1																
	Uric acid				0.18	0.30	0.80		0.71	0.24										
	Convulsion				3															
	Uric acid				0.74	0.45	1.04	0.37	0.06	0.18	0.31	0.59	0.52	0.39	0.27	0.65	0.31	0.36	0.38	
Average uric acid		0.38	0.27		0.44	0.59	0.80	0.44	0.38	0.39	0.47	0.55	0.47	0.35	0.28	0.65	0.31	0.33	0.38	0.29

We have had an opportunity to study a patient with pre-eclampsia over a period of a month. During that time 21 blood specimens were obtained and analyzed for nonprotein nitrogen, urea nitrogen, uric acid, chlorides, CO_2-combining power and sugar. Twenty-four-hour specimens of urine were analyzed for uric acid. In Chart 9 are shown the findings for blood nonprotein nitrogen and uric acid and for urine uric acid. The other constituents determined are not shown in the chart, as they were wholly within normal limits. A study of the patient's past history, antenatal course in this pregnancy, blood pressure, albuminuria, edema, eye ground findings and symptoms, leaves no doubt that she is suffering from pre-eclampsia. The patient is still undelivered and about three weeks from term (April, 1938). The chart of this pre-eclamptic patient reveals an elevation of blood uric acid which is constant and persistent, although the hypertension, albuminuria, edema, and symptoms had responded to treatment. The nonprotein nitrogen of the blood is at the upper limits of normal while the excretion of uric acid is within normal range and certainly not decreased. The diet has been uniform and purine-free during the major part of the period of study.

We regard pre-eclampsia as the same disease entity as eclampsia, differing from the latter only in that it is not accompanied by convulsions. However, pre-eclampsia usually eventuates into eclampsia, unless the patient responds to treatment, whether that be sedation or delivery. Viewing pre-eclampsia, then, as a mild or early stage of actual eclampsia the persistent elevated blood uric acid curve in this last chart assumes a certain significance with respect to the metabolic disturbance which may be the basis of the development of eclampsia. This change in uric acid metabolism occurring previous to the outbreak of eclamptic convulsions and resulting in a high blood uric acid, due either to increased formation, or more likely, to decreased destruction of uric acid in the liver, is thus far the earliest perversion of metabolism noted in the development of eclampsia. Normal pregnancy is accompanied by certain marked changes in metabolism, such as, among others, a lowering of the total base, an increase in total lipids and decrease in the CO_2-combining power of the blood and a depression of urea in both the blood and urine. However, these changes are not any more pronounced in eclampsia.

We finally present Chart 10, which shows the values for nonprotein nitrogen and uric acid in the blood of a fatal case of eclampsia. The autopsy findings in this case showed the kidneys to be normal and the liver to have peripheral necrosis of the lobules. The autopsy report reads as follows: "*Liver:* The liver weighs 1,450 gm. The capsule is smooth and glistening. The liver is slightly softer than normal. The external surface of the liver is a light reddish brown mottled with a few small areas of red mainly over the surface of the right lobe. On cut section the cut surface is a light brown mottled with minute areas of red. Scattered throughout the liver substance are a few areas of grayish yellow in which the liver architecture is lost. These areas measure from 1 to 2 cm. across.

"*Kidneys:* The right kidney weighs 135 gm., and the left 140 gm. The capsule of the right kidney is smooth and glistening and strips with ease. The external surface of the right kidney is a pale pinkish brown. On cut section the cut surface is a pale pinkish red. The cortex is of normal thickness and sharply demarcated from the medulla. The mucosa of the pelvis of the right kidney is slightly thickened and presents areas of red in which the mucosa is granular. The right ureter is slightly dilated. The left kidney is similar to the right. The left pelvis and ureter are normal." The curves in Chart 10 show the nonprotein nitrogen to be within normal limits, excepting immediately before death, when there was a slight elevation

to 48 mg. per 100 c.c. of blood. The uric acid, on the other hand, was elevated throughout the period of study and rose to approximately three times the normal value. As the postmortem examination revealed normal kidneys and the blood analyses showed no nitrogenous retention during the first two days of the disease, it would appear that the elevated uric acid in the blood was not due to lowered kidney excretion of this substance.

DISCUSSION

From the findings presented above, it seems to us, that the increased blood uric acid in eclampsia cannot be explained on the basis of decreased excretion by the kidneys. It is also noteworthy that the increase in blood uric acid appears as one of the early signs of the

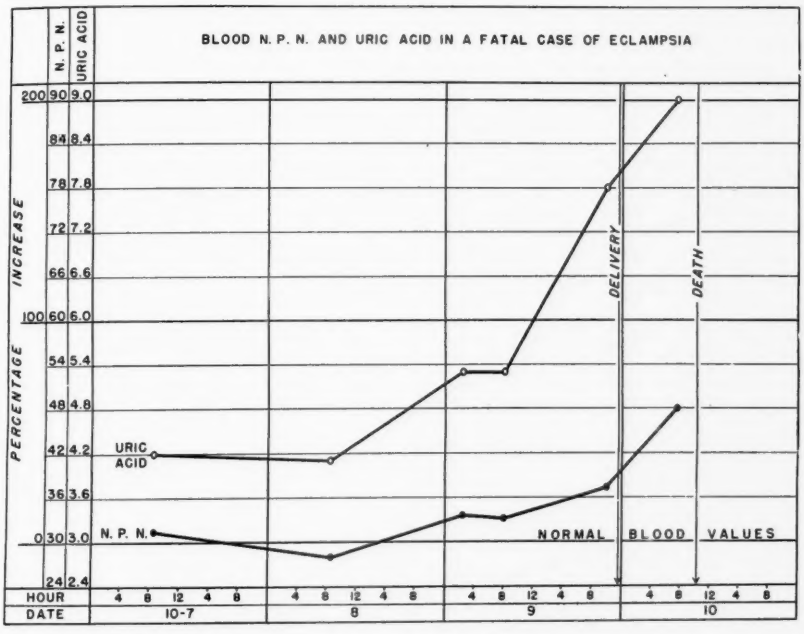

Chart 10.—Blood nonprotein nitrogen and uric acid in a fatal case of eclampsia.

disease, whereas kidney manifestations, such as nitrogenous retention as shown by the nonprotein nitrogen and urea values, appear late, if at all, in the course of the disease. There can be no doubt regarding the existence, in some fatal cases, of a typical "kidney of eclampsia," as described by Bell. However, all patients dying from eclampsia do not show these typical kidney lesions, which is further evidence that the kidney plays no etiologic role in the production of eclampsia. From the autopsy examination of the patient referred to above, whose nonprotein nitrogen and uric acid values are shown in Chart 10, it would seem wholly improbable that the kidneys played any role, not only in the etiology of the disease, but also in her death.

What then is the cause of the elevated uric acid in the blood of the eclamptic patient? An exogenous source seems definitely ruled out,

when we bear in mind that the eclamptic patient is usually taking no food by mouth during the time of the acute illness, a period during which the blood uric acid may be steadily rising.

We have referred to factors which decrease uric acid elimination. These include certain aromatic acids, ketosis and high lactic acid concentrations. Eclampsia, as shown by Stander and Radelet,[13] is associated with increased blood lactic acid, but if this elevation affects mainly the kidney excretion of uric acid, as Quick found, our results would indicate that an increased blood lactic acid is probably not the factor producing high blood uric acid in eclampsia.

If we assume, as indicated above, that from 30 to 50 or 70 per cent of the uric acid formed in the body is destroyed in the liver, it is a logical supposition that in eclampsia this destruction of uric acid may be interfered with. Should this be the case, the increased blood uric acid in the face of normal kidney excretion of this substance, becomes understandable. Mann and his co-workers found that in dogs, with complete extirpation of the liver, there is a marked accumulation of uric acid due, they believe, to the abolition of uricolysis. We must, however, be careful in the interpretation of these animal experiments, when considering uric acid metabolism in the human, being, for the reason that in the dog, unlike in man, there is normally almost complete uricolysis, and only traces of uric acid can be found in the blood stream. Nevertheless, Mann's work gives indirect support to the theory of decreased uric acid destruction in the liver where this organ is diseased or involved, as in eclampsia or chloroform poisoning. It is interesting to note that in a fatal case of acute yellow atrophy with marked impairment of deaminization, Rabinowitz found a normal blood uric acid value. Is it possible that here uric acid formation, as well as its destruction, was greatly reduced?

SUMMARY

A study of 5 cases of eclampsia shows that this disease is not associated with decreased excretion of uric acid and that the high blood uric acid, which invariably accompanies the disease, is probably due to impaired destruction of this substance in the liver. This impairment in hepatic destruction of uric acid appears early in the disease and may perhaps be of assistance in our search for the etiology of eclampsia. In any event, it appears as additional evidence that eclampsia is the outcome of a metabolic disturbance, and probably in one or other phase of nitrogen metabolism.

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THE EFFECTS ON THE BLOOD FROM INJECTIONS OF ENDOCRINE PRINCIPLES IN THE FEMALE

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A REVIEW of the literature conveys the lack of information concerning the study of the blood changes in connection with the administration of endocrine principles in the human being. In the past, investigation has been confined to animal experimentation.

1. Hans Scheerer studied parental injections of different hormones in animals and human beings by consecutive studies of the reticulocyte count in the circulating blood per 1,000 erythrocytes, as found in a cover glass specimen after preparation with an alcohol-azure solution. The counts were made one, two, three, five, and twenty-four hours after the injection. Special attention was paid to a possible "shift to the left of the reticulocytes" which permits differentiation of true increase in erythropoieses from mere increased liberation of reticulocytes from the bone marrow into the blood stream. He refers to a rise which increases in proportion to the amount of administered hormone units as "hormone specific." Following a test of ten different extracts, only those which primarily or secondarily acted on the sympathetic system such as the thyroid, adrenals and anterior lobe of the pituitary gland, caused a true specific rise in the reticulocytes. This was believed to be produced through increase in the blood volume circulating through the bone marrow cells, or by direct action of the sympathetic nerve fibers which enter the bone along the nutritive vessels to the bone marrow cells. In all instances the reticulocytosis produced by the anterior pituitary hormone was believed to be identical with marked physiologic reticulocytosis of pregnancy.

2. Meyer, Stewart, Thewlis and Rusch call attention to the fact that it has long been known that under certain conditions of oxygen want, there regularly occur hyperplasia of the bone marrow and an increase in hemoglobin, erythrocytes, and reticulocytes in the peripheral blood. They believe that if the pituitary furnished a hormone which affected the erythrogenic tissues, the response in the hypophysectomized animals to diminution in oxygen tension of the erythrogenic tissues might be deficient in one or more respects. They found that hypophysectomy in rats invariably is followed by anemia and a significantly subnormal reticulocyte count. The stimulus of reduced oxygen tension of the tissues is not followed by reticulocytosis or bone marrow hyperplasia in hypophysectomized rats, whereas this is constant in normal animals. There is, however, increase in erythrocytes and hemoglobin under stimulation of oxygen want if the stimulus is applied within ten days after hypophysectomy, but none if the rats are exposed twenty-five days or more after operation. They believe that this discrepancy is due to a temporary persistence of some pituitary hormone, though the reticulocytes are not increased as a result of oxygen want or the administration of liver extract. They further found that the administration of antuitrin growth hormone and anterior pituitary extract (G. A. P.) which is deficient in the thyrotropic and gonadotropic substances, to hypophysectomized rats, is followed by sharp, invariable increase in the erythrocytes. The authors conclude that the pituitary probably affects erythropoieses. It is their impression that the results probably depend on a hormone action.

3. Stodtmeister studied the blood changes in hypophysectomized dogs and the effect of the pituitary extracts on the hemopoietic system. He refers to the fact that most investigators found decrease in hemoglobin and erythrocytes following hypophysectomy.

HISTORY OF INVESTIGATION

A more thorough understanding of the action of endocrine principles in the female patient was suggested by the recognition of hypochromic anemia in cases showing endocrine imbalance.

Women, commonly, never seem to maintain a normal concentration of hemoglobin and this deviation from the normal usually occurs between 25 and 45 years of age. Such variation does not seem to occur in the male.

This leads one to inquire: Why do so many imbalanced glandular cases become anemic, and why are they more numerous in women between 25 and 45 years of age?

With the knowledge of the heightened functions of the different endocrine glands concerned in the different stages of female life, and the common existence of hypochromic anemia, there should be no hesitancy in associating some interrelationship between the endocrine system and the stability of the hemopoietic system.

The endocrine system must certainly be at a disadvantage in maintaining its balance before and after the advent of menstruation, and in later years, its regulation. Finally, it may be subjected to the increased demands and insults exigeant of their functions during pregnancies.

During the recognition and treatment of the syndrome commonly referred to as menopausal in type, it was found that hypochromic anemia in varying degrees accompanied 90 per cent of the cases.

The blood picture of hypochromic anemia has shown improvement in the majority of cases by injections of liver. In my experience, these results, as a rule, are but temporary. The blood count soon returns to its former level. A second course of injections failed to give as marked response as the first, and with the same resulting recession.

Many forms of liver, iron, combinations of iron and copper, vitamins, ventriculin, hydrochloric acid, etc., were resorted to orally, with the hope of maintaining the seemingly satisfactory response from the injections of liver. Difficulty was experienced in maintaining the improved level and in a number of cases the drop in hemoglobin was lower than previous to the injections.

MATERIAL

The material comprises a thorough four-year study of 30 private patients, women of intelligence, ranging in ages from 17 to 64 years. Each was known to have a definite hypochromic anemia and syndrome of symptoms indicative of a marked glandular imbalance. In the interim, several hundred patients have been treated and the interpretation of complete blood counts is presented in Table I.

SYNDROME

The syndrome of symptoms, in the cases referred to, are a well-defined group. They represent the experience of a great many females. A number of symptoms occurring at 45 years of age are designated as menopausal for want of a better term.

While these symptoms are associated with the climacteric, it is believed they should be classed as a syndrome resulting from failure or an interruption of the normal interrelationship of the pituitary, thyroid, ovary, and adrenals. They are more definitely interpreted as a syndrome resulting from a slow and insiduous change in the glandular imbalance which takes place between adolescence and 45 years of age. Such syndrome may be present at any age and its prominence is indicative of the degree of imbalance of the functions involved.

Postoccipital headache, melancholia, discontent, marked pessimism, sobbing, depression, vertigo, and insomnia are fairly constant in the signification of this disturbance.

Hot flushes have been noted with less frequency than the above classification unless the 45-year age limit is reached and are observed as a rule when sudden ovarian failure takes place from destruction or removal of both ovaries.

Pregnancy frequently is an injurious factor relative to the efficiency of the different glands. Maternal glandular activity is so accelerated during fetal development that endocrine principles are increased to a level surpassing that formerly experienced, enabling many females to enjoy the most healthful time of their life. A variable time ensues following either the first, second or third postgestation period when a depleted function is conspicuous by the advent of the syndrome.

By taking a thorough history of each patient, one can learn when the onset of the first appearance of such syndrome occurred and subsequent to which particular pregnancy.

Furthermore, I have frequently observed the same disturbance after the removal of the entire uterus where the ovaries have been preserved.

TREATMENT

The first routine adopted, each individual received injections of progynon for six consecutive days totaling 2,250 R. U. Following this, injections of anterior pituitary-like principle (A. P. L. or antophysin) 100 R. U. twice weekly until 1,000 R. U. were given. Complete blood counts were taken previous to and following the entire course of treatment.

Considerable enthusiasm was created because a certain group of cases showed an immediate response of from 10 to 20 per cent in the improvement of the hemoglobin and a corresponding increase in the erythrocyte count.

An interesting observation followed this improvement. An effort was made to maintain the improved blood picture by resorting to the previously mentioned method of administering orally numerous forms of iron, liver and iron combinations, ventriculin, etc. In a number of cases the blood count returned to the low level which existed prior to endocrine treatment.

In the cases where the response from the endocrine administration was not maintained after oral medication, the repeating of the former endocrine principles by injection caused the hemoglobin to again return to near normal limits.

In the greater majority of patients treated, it has been necessary to repeat the course of hypodermic injections due to the return of the syndrome. It has been noted at this time that there is a corresponding recession of near 50 per cent from the former improved state of the blood. The repetition of treatment is usually advisable in four to six months. After repeating the same course of treatment, symptoms disappear for the second period lasting from seven to ten months. Further repetition of the treatment has kept a greater number of patients free from symptoms for a longer period of time, lasting from twelve to eighteen months.

TABLE I

A. EFFECTS ON HEMOGLOBIN AND ERYTHROCYTES

ESTROGEN AND PITUITARY-LIKE PRINCIPLES

*INCREASE		AGE	*DECREASE	
EST.	PIT.		EST.	PIT.
50%	73%	Under 45 years	50%	27%
62½%	83%	Above 45 years	37½%	17%

B. EFFECTS ON LEUCOCYTES

54½%	45½%	Under 45 years	45½%	54½%
25%	100%	Above 45 years	75%	0%

*The increase or decrease signifies from 10 to 20 per cent.

Following the course of injections of endocrine principles, a well-balanced combination of glands, consisting of ovary, thyroid, and anterior pituitary, is administered orally. The dosage of each ingredient is arranged suitable to the patient's requirements. Continuous and indefinite administration is insisted upon. This treatment is given with the thought that certain glandular principles of undetermined recognition would be conducive in maintaining the level of the blood improved by the injections or replacements of the endocrine principles.

The blood picture has presented a more satisfactory stabilization when orally administered glands are given after the injection of endocrine principles.

In addition to the encouraging results first noted, another phase of great interest was the recognition of certain individuals who exhibited a definite menopausal syndrome, yet experienced an entirely opposite effect on the blood picture than the ones which were benefited. These negative and seemingly detrimental effects were observed and corroborated by the lowering of the blood count. It has been perplexing to reason why two individuals, much alike physically and with a syndrome similar, experience two different extremes as indicated by the blood counts and modification of relief of the syndromal symptoms.

In an attempt to explain this intrusion of glandular interrelationship, a second routine was adopted whereby blood counts were taken previous to and following the administration of each of the two different principles. The results of this observation conveyed valuable information.

The hemoglobin and erythrocyte count was increased by progynon and decreased by anterior pituitary-like principle or antophysin in a group of cases. In another group, an opposite effect, a decrease of hemoglobin and erythrocyte count by the administration of progynon and an increase following anterior pituitary-like principle or antophysin.

The effects on the blood picture of all cases, as demonstrated by the white blood cell and neutrophile counts, are quite interesting.

Age seems an important consideration with regard to the action of estrogen and pituitary-like principles on the leucocytes. After 45 years of age, estrogen produces an antagonistic action on the leucocyte mechanism, causing a leucopenia while the pituitary principle is just as prominent in creating an increase or a leucocytosis. This action is noticeably opposite in patients previous to 45 years of age.

SUMMARY

In review of the complex and changeable results in the blood counts of a series of females showing endocrine imbalance, one is confronted with the different effects on the hemoglobin, erythrocytes, leucocytes and neutrophile counts from the injection of the different commercial endocrines.

It would seem courageous to attempt to evaluate such action and proves rather conclusively that each individual must be studied separately as to what constitutes the imbalance. This entails a complicated determination of the percentages of endocrine principles which are to be considered normal; the percentage of endocrine principles which would be necessary at different times to equal the normal balance; an illustration of which would be the changeable amounts of principles produced during the menstrual cycle. In the administration of a principle corresponding to the least deficient, an oversupply may be produced and in some unexplainable manner, either an anti-action or obscure action might be brought about to produce an especial detrimental effect on the blood mechanism.

Seventy-six and one-half per cent of the patients were improved by the injections of the pituitary-like principle. Sixty per cent of the patients responded to estrogen favorably.

TABLE II. TABULATION OF EFFECTS ON THE BLOOD FROM INJECTIONS OF ESTROGEN OR ANTERIOR PITUITARY-LIKE PRINCIPLES

AGE	HEMOGLOBIN				R. B. C.				W. B. C.				NEUTROPHILE			
	INCREASE		DECREASE		INCREASE		DECREASE		INCREASE		DECREASE		INCREASE		DECREASE	
	EST.	PIT.	EST.	PIT.	EST.	PIT.	EST.	PIT.	EST.	PIT.	EST.	PIT.	EST.	PIT.	EST.	PIT.
Under Forty-Five Years of Age																
17		1				1						1		1		
18		1				1				1				1		
23	0	1	0			1	1		1			1	1			1
28			1		1				1				1			
29	1			1	0	0	0	0		1	1		1	1		
30	1						1		1				1			
30			1	1	0		0	1	1			1			1	1
30	1				1						1				1	
31	1	1			1	1					1	1		1	1	
33		1	1			0	1	0		1	1			1	1	
39	0	1	0		1	1					1	1		1	1	
39			1	1			1	1	1			1	1			1
42	1				1				1				1			
42		1				1				1				1		
42		1	1				1	1	0	1	0		1			0
Above Forty-Five Years of Age																
45	1				1						1				1	
47	1	1			1	1			1	1				1	1	
49		1				0		0		0		0				1
50	1				1						1		1			
54	0		0	1			1	1		1	1		1	1		
57	1				1						1		1			
58		0	1	0		1	1			1	1				1	1
63	1	1			1	1			1	1			1	1		
64		1	1			1	1			1	1				1	1

In 23.5 per cent of the patients, the percentage of hemoglobin and the erythrocyte count were decreased by the pituitary-like principle. Forty per cent of the cases were decreased by the action of estrogen.

One patient, not included in the above percentages, experienced a definite lowering of the hemoglobin and erythrocyte count from the administration of estrogen and after an interval of time, a further lowering from the administration of the pituitary-like principle. The reactions in this case were marked and caused aggravation of the syndrome.

Separate consideration is necessary so that the action of the individual patient should be the criterion for the final determination of the selection, time and amount of the endocrine principle to be administered in the treatment of endocrine imbalance.

The administration of one principle may cause a decline in the percentage of hemoglobin and the erythrocyte count, only to reverse the picture on replacing a different principle which produces a definite response higher than the initial count.

Just what effect may be produced from a possible oversupply of any one principle necessitates careful consideration. When one thinks of the toxicity attendant with the disturbed function of the thyroid gland, it seems logical to assume that any one of the other internal secreting glands may be disturbed to the point of producing detrimental effects. The lack of knowledge of the continuous variations and interruptions in the supply of the different principles in each individual creates a complicated and confusing problem.

The almost daily changeable functional supply of the different glandular principles, occurring at different periods during the monthly cycle of the female, is illustrative of what seems to create an obstacle in the determination of the amount of any principle to be administered without the possibility of producing an imbalance with injurious results in a certain proportion of endocrine cases.

The effect on the blood mechanism in a certain group of endocrine cases justifies suspicion of some obscure detrimental action in contrast to a decided beneficial effect in another group. There may be justification for assuming that the imbalance of different endocrines and hypochromic anemia are closely associated and that a specific action on the hemopoietic system does exist.

The study of repeated complete blood counts, before and after a number of injections of each principle, properly timed, offers considerable valuable information which may create more accuracy and satisfaction in the selection of the specific endocrine principle to be employed and the time and amount advisable in each individual.

CONCLUSIONS

1. A definite syndrome of symptoms is indicative of a slow and insidious failure of the glands of the endocrine system in the female and occurs at any age.

2. The endocrine system is related in some specific manner in the maintaining and stabilization of the hemoglobin and erythrocyte count of the blood.

3. Maintenance of hemoglobin and erythrocyte count often is accomplished more satisfactorily after replacement of endocrine principles.

4. Increased accuracy in the determination of the principle and dosage to be given hypodermically and the relief of syndrome is obtained by complete blood counts before and after the administration of each endocrine principle.

5. Endocrine patients should not be treated with endocrine principles unless a study of the blood is made at the same time.

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PREGNANCY COMPLICATED BY SICKLE CELL ANEMIA

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SICKLE cell anemia as a complication of pregnancy has been reported five times in the literature since the first description of the disease in 1910.[1] We wish to present two additional cases of acute sickle cell anemia in pregnancy, and to discuss some problems of diagnosis and management.

The discovery of the sickling trait was first made by Dresbach[2] in 1904, when a negro medical student submitted a sketch of his own blood during a course in histology. The acute phase of the disease was first described by Herrick[1] in 1910. The name "sickle cell anemia" was applied to the anemic phase by V. R. Mason[3] in 1922, and the term "sicklemia" used to designate the asymptomatic sickle cell trait which may be found in 7 or 8 per cent of the colored race. Over eighty articles have been published on the subject since that time. Sydenstricker,[4] literature. Sydenstricker[7] was the first to mention an instance of sickle cell anemia in pregnancy.

Yater and Mollari[8] record the details of a 25-year-old negro woman, six months pregnant, who died of the disease and was autopsied three weeks after spontaneous abortion. Death occurred during an "abdominal crisis." This was her second pregnancy, the first having terminated as a spontaneous abortion at six months. The third case was reported by Lash,[9] whose patient was a 21-year-old colored primipara at term, dying in shock six hours following cesarean section. The diagnosis was made at autopsy. Richter and others[10] mention the occurrence of a normal delivery in a 16-year-old colored primipara with sickle cell anemia, diagnosed on the tenth post-partum day. The patient apparently responded well to liver therapy. The fifth case was reported by Lewis,[11] whose patient was a 25-year-old negro woman giving a history of three spontaneous abortions. The diagnosis of sickle cell anemia was made when she was three months pregnant, and a hysterectomy and sterilization were done. Lewis feels that the disease is an indication for the termination of pregnancy.

Although the disease has been described in great detail by numerous writers,[4-6] it may be pertinent to summarize very briefly the salient features. Both sicklemia and sickle cell anemia are congenital and hereditary diseases, transmitted through either sex as a dominant Mendelian factor, and occurring almost exclusively in the negro race. The latent trait, or sicklemia, is characterized by the peculiar "oat" or "sickle" shapes assumed by the red blood cells when removed from the circulation and maintained in a sealed preparation under reduced oxygen tension. The reaction is reversible, for the cells may assume their normal shape if the preparation is oxygenated,[12] and experimental work has shown that the same reactions may take place in vivo.[13] Sicklemia is entirely symptomless, and women who have this trait frequently give normal obstetric histories.

Sickle cell anemia, on the other hand, is a less common entity, very rare in pregnancy, and characterized by hemolytic relapses and remissions, severe anemia, the sickling phenomenon often on fresh smears, and symptoms of weakness, muscular and joint pains, jaundice, and a tendency for vascular thromboses. There may be leg ulcers and acute abdominal crises, possibly due to thrombosis of abdominal vessels. Individuals with the disease are often of poor physique, succumb readily to slight infections, and rarely live past thirty years of age. There is no specific treatment. The characteristic findings at autopsy are essentially the same as those described below (Case 2). During childhood, the spleen may be greatly enlarged, but later the constant destruction of pools of sickle cells with the deposition of hemosiderin, together with infarction and fibrosis, may reduce the size of the spleen.

REPORT OF CASES

CASE 1.—Mrs. A. C., a colored primigravida, aged 19 years, entered the hospital on Sept. 15, 1935, complaining of generalized weakness and joint pains.

There were no familial diatheses. The only past illnesses had been frequent colds and "rheumatic attacks," and pneumonia. The patient was now over eight months pregnant, the last menstrual period having occurred Jan. 1, 1935. She had been attending an outpatient maternity clinic for prenatal care, and during the past month had been placed on a fat-free diet because of epigastric pain and jaundice, although there was no other evidence of gall bladder disease. She had been subject to joint pains, particularly in the knees and elbows at various intervals. During the past week she had remained in bed because of progressive weakness, jaundice, and anorexia. She reported some recent weight loss.

The significant findings on physical examination were a marked icteric tint to the skin and sclerae, with pallor of the mucous membranes. Temperature, 99.4° F.; pulse, 96; respiration, 20; blood pressure, 120/80. The tonsils were large and infected. The heart and lungs were not remarkable. The liver was enlarged, the edge being palpated two fingerbreadths below the costal margin. There was considerable epigastric tenderness. The spleen was not palpable. The height of the uterine fundus was 30 cm. above the symphysis pubis. The fetus was in left occipitoposterior position, and the fetal heart tones were regular, with a rate of 130. All pelvic measurements were within normal limits. No peripheral edema was noted.

The urine was deeply bile stained; specific gravity, 1.018, sugar and acetone, negative; 0.6 gm. albumin per liter. Microscopic examination showed a few pus cells, but no red blood cells or casts. The initial blood count showed 40 per cent hemoglobin and 1,800,000 red blood cells. The white cell count was 11,000, with 87 per cent neutrophiles. Sedimentation time, 18 mm. fall in twenty-five minutes. Blood Wassermann and Kahn negative.

The clinical impressions on entry were (1) primigravida, three weeks from term, not in labor; (2) probable toxic hepatitis, either due to early acute yellow atrophy or catarrhal jaundice; and (3) moderately severe anemia, unexplained.

About twelve hours after admission she was re-examined with identical findings. It was felt at this time, in view of her race, the anemia, and the history of joint pains and jaundice, that sickle cell anemia should be considered; hence a complete hemogram and studies of blood chemistry were requested.

The laboratory reports were as follows: Hemoglobin, 42 per cent (Sahli); erythrocytes, 1,660,000; color index, 1.30; leucocytes, 18,850, with 72 per cent neutrophiles, 25 per cent lymphocytes, and 3 per cent monocytes. Marked anisocytosis and poikilocytosis, with marked polychromasia. There was some basophilic stippling and many Jolly bodies. Normoblasts 66 per 100 leucocytes. There was marked sickling of the red cells. Reticulocyte count was 23 per cent. Fragility test, initial hemolysis at 0.28; hemolysis not complete at 0.24. Hanging drop showed marked sickling of the red blood cells after eighteen hours.

Blood Chemistry.—Nonprotein nitrogen, 22 mg. per cent; urea nitrogen, 9.5 mg. per cent; uric acid, 4.2 mg. per cent; carbon dioxide combining power, 48 volumes per cent; van den Bergh test gave a prompt positive direct reaction, and an indirect quantitative bilirubin of 20 mg. per cent. Blood cholesterol, 200 mg. per cent; icterus index, 250 units.

On the basis of these findings the diagnosis was revised to pregnancy complicated by sickle cell anemia, and the patient was started on a high caloric liver diet, with reduced iron and copper medication.

During her six weeks' stay in the hospital, 7 transfusions, each of 500 c.c. of blood, were given both by the direct and the indirect citrate methods. On October

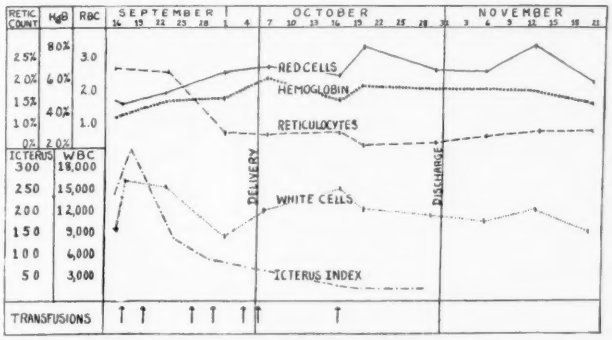

Fig. 1.—Chart showing hematologic findings (Case 1).

20, 3 capsules of Lextron (Lilly) three times a day were substituted for the reduced iron and copper; otherwise there was no alteration of treatment. Eleven hemograms and repeated chemical examinations of the blood were made at regular intervals. To conserve space, the hemograms are presented in graphic form in Fig. 1. With the exception of the van den Bergh tests and icterus index, the remaining chemical determinations did not vary significantly from the values given above. The direct van den Bergh showed a prompt positive response in seven determinations, although the jaundice was probably of a hemolytic type. The bilirubin value fell gradually from 20 mg. per cent to 2.2 mg. per cent. The icteric index, as shown in Fig. 1, was 250 units on admission, rose to 350 units on the third day after admission, then gradually fell to 40 units over a period of six weeks.

During the first week there was marked improvement in the patient's general condition, and all symptoms subsided. There appeared to be no indications for induction of labor. On October 6 (the estimated date due), labor began spontaneously, and after a first stage of only three hours, there was a normal spontaneous delivery of a living, 6 pound 11 ounce male infant. Episiotomy was not done and vaginal examinations were eliminated in order to avoid all chance of potential infection. The measured blood loss was 150 c.c. A sealed wet mount of blood from the umbilical cord demonstrated no sickling of the red blood cells after twelve hours.

The patient's father, sister, and two half-brothers were examined for sicklemia and all were negative. The mother, however, showed definite sickling of the red blood cells in the sealed hanging drop, but none on the fresh smear. The baby was re-examined after one month and no sicklemia was found.

During the puerperium the patient remained in good clinical condition and became ambulatory on the sixteenth post-partum day. The highest temperature recorded following delivery was 99.2° F., excluding one rise from a transfusion reaction on the eleventh post-partum day. X-ray plates of her legs, arms, and skull showed no abnormalities of bony structures. She was discharged from the hospital on October 31, at which time a physical examination revealed no unusual findings.

Five follow-up examinations were made, the last on May 26, 1936 (seven months post partum). At no time were there any complaints referable to the anemia. The hemoglobin varied between 48 and 54 per cent, and the red cell count between 2.0 and 2.35 million. The baby remained in good condition.

CASE 2.—Mrs. L. S., a colored female, aged 20 years, entered the hospital at 6:00 P.M. on April 22, 1935, complaining of pains in the chest.

Her general health had been good until the onset of the present illness. She was subject to frequent colds, but none had been serious. There was no history of joint pains, anemia or jaundice. Both her mother and father were living and well. There had been no previous pregnancies.

The last normal menstrual period began on Nov. 22, 1934, and she stated that she was now five months pregnant, and had felt life for three weeks. About four weeks ago she caught a "cold" which confined her to bed, and was characterized by cough, weakness, and malaise. These symptoms persisted until five days ago, when she noticed chest pains, chilly sensations, difficulty in breathing, nausea and vomiting, and a hacking cough. Two days ago she began to spit up blood-tinged mucus. The symptoms became gradually worse until entry to the hospital.

The physical examination revealed a fairly-well developed, colored female appearing to be acutely ill. There was a distinct icteric tinge to the sclerae, and rapid and labored breathing. The rectal temperature was 101° F., pulse 160, and respirations 36. Blood pressure, 115/70. The tongue was dry and coated. The anterior cervical glands were enlarged, but not tender. The heart did not appear to be enlarged; the sounds were rapid, but regular and without murmurs. There were areas of dullness at both bases, with bronchial breath sounds, suggestive of bilateral consolidation. The abdomen was distended, but soft, and there was a symmetrical soft mass rising to the level of the umbilicus. Fetal heart tones could not be heard. There was tenderness in both flanks, especially on the right. The pelvic findings were consistent with a five and a half to six months' pregnancy, the size of the uterus appearing to be larger than the duration of amenorrhea would indicate.

Examination of the blood revealed 35 per cent hemoglobin; red blood cell count, 1,920,000; color index, 0.92; white cell count, 47,800, with 87.5 per cent neutrophiles, 3.0 per cent lymphocytes, 9.0 per cent monocytes, and 0.5 per cent myelocytes. The platelets appeared normal. There was marked anisocytosis, and poikilocytosis, with some polychromasia. There were 5 nucleated red blood cells for each 100 leucocytes. Examination of fresh mount for sickling phenomenon was not done.

There were no significant findings in the urine.

The clinical impressions were: (1) bilateral bronchopneumonia; (2) five and one-half to six months' pregnancy; (3) possible macrocytic primary anemia of pregnancy (in view of color index of 0.92), undetermined type; and (4) unexplained jaundice.

There was a rapid downhill course, with death occurring twenty-two hours after admission.

Autopsy was performed by Dr. L. J. Tragerman, who has kindly submitted the following summary of the essential pathologic findings:

Autopsy was performed nineteen hours after death. The body was that of a well-developed and nourished colored female. No abnormalities were noted in the cranial cavity. Heart weighed 420 gm.; the valves and myocardium appeared normal throughout. The chambers of the heart as well as many of the blood vessels throughout the body, particularly the pulmonary arteries, inferior vena cava, portal system, pelvic veins and many of the major aortic branches were

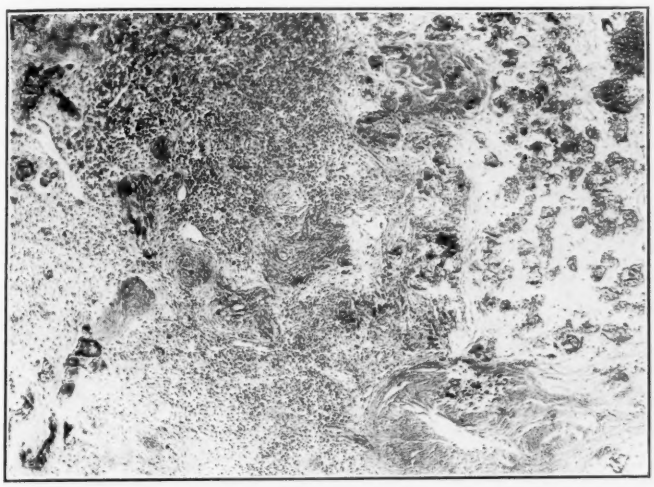

Fig. 2.—Photomicrograph of spleen. Note extreme siderofibrosis and pools of blood. (×95.)

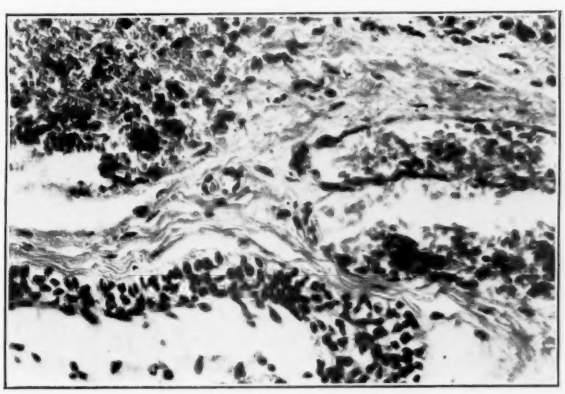

Fig. 3.—Section of placenta (×645) showing sickling of cells in maternal blood sinus. Note sickle cells in capillaries.

partially filled with a stringy, loose, red-brown clot, appearing recently ante mortem. The right lung weighed 660 gm.; upper lobe appeared normal and middle and lower lobes contained numerous hemorrhagic infarcts, varying up to 2 cm. in maximum diameter. In many of the branches of the lower lobe there was present firm, gray-pink thrombotic material. Left lung weighed 670 gm. The upper lobe appeared normal. The lower lobe contained numerous small hemorrhagic infarcts similar to those present in the right lower lobe. The peritoneal cavity, gastrointestinal tract, liver, pancreas, and adrenals were essentially normal. The spleen was unusually small, measuring about 3 cm. in its broadest capsular surface,

and weighed close to 20 gm. Capsule was smooth and mottled purple gray, and was slightly thicker than normal. Surfaces made by section were firmer than normal and of variegated green-gray and pink-brown color with completely obscured Malpighian markings. Kidneys together weighed 490 gm. and were of equal size and similar gross appearance. Capsule stripped with some difficulty from a dull brown surface and the cut surface markings were obscure. Kidney pelves and ureters were moderately dilated. The lower urinary tract was normal. Cervix was closed, soft and smooth. The body of the uterus was enlarged, consistent with pregnancy, and its cavity contained a normally attached placenta, amniotic sacs and well-developed twin fetuses, each about 20 cm. in length.

The only abnormality in the adnexal structures was the presence of numerous firm, gray-brown to red thrombi, not adherent to the walls of the veins in the broad ligament. The bone marrow in the lower end of the femur and in the tibia was bright red.

Histologic examination confirmed the presence of hemorrhagic infarcts in the lungs, with an associated early bronchopneumonia and revealed the presence of deformed erythrocytes, many of them typically sickled, in virtually all the maternal blood vessels examined. Ante-mortem thrombi were seen in the pelvic veins with sickle cells packed into the margins of the thrombi. The spleen (Fig. 2) showed the most striking alteration in histologic appearance. The capsule was thickened by a dense fibrous tissue in which some infiltration with iron pigment was present. Pulp sinusoids were distended with packed, distorted erythrocytes, all showing some degree of sickling. In addition there were scattered perifollicular hemorrhages. Many areas were almost completely avascular, showing a severe degree of siderofibrosis with hyalinization and thickening of both the Malpighian corpuscles and trabeculae, and deposition of large quantities of pigment material confirmed by special stain to contain iron. Liver showed cloudy swelling, slight iron pigmentation and numerous sickle cells in the sinusoids. In the kidney the glomerular tufts were made prominent by clumps of sickle cells. Cloudy swelling of the tubular epithelium was present. Impression smear of the tibial marrow (Wright stain) showed moderate hyperplasia, predominantly of erythrogenetic elements.

The veins in the uterine wall showed many sickle cells as did the maternal vessels in the placenta (Fig. 3). Capillaries seen in the chorionic villi showed normal erythrocytes. Sections of the fetal organs of both the male and female fetuses showed no deformity of erythrocytes beyond that usually seen in formalin fixed tissue. There were hematopoietic foci in the liver with normally-shaped erythrocytes. The umbilical vein of the female fetus showed a few deformed erythrocytes on section, but no definite sickled cells.

Anatomic Diagnosis.—(1) Sickle cell anemia; (2) thrombophlebitis, pelvic veins; (3) embolism, pulmonary arteries, with multiple infarcts; (4) pregnancy, twins, five months; and (5) siderofibrosis, spleen, severe.

DISCUSSION

Of the seven cases now reported where pregnancy occurred with sickle cell anemia, 3 patients died and only two progressed to an uneventful delivery. While the course of pregnancy and delivery may be entirely normal from an obstetrical standpoint, gestation does appear to exert an unfavorable influence upon women with the disease. In fact, the reduced alkali reserve and reduced oxygenation of blood which may accompany pregnancy, and which favor the sickling phenomenon experimentally[12, 13] may be factors in the production of the acute phase, although this is entirely hypothetical. If the patient improves with repeated blood transfusions and the usual antianemic measures, she may be successfully carried to term. Extraordinary precautions should be taken to avoid infections at the time of delivery, and to conserve blood.

It is difficult to explain the tendency to the thromboses, which directly led to death in our second patient. Diggs[6] believes that the abnormal shape of the red blood cells may act mechanically to block the vessels. Possibly the congestion of pelvic vessels accompanying the pregnancy was an additional factor. The

multiple infarcts of the lungs, apparently embolic from the pelvic veins, led to a clinical diagnosis of bronchopneumonia. In the first case, the jaundice, severe anemia, and joint pains in a negro woman led to the diagnosis of sickle cell anemia, confirmed by blood studies. The diagnosis of sickle cell anemia is easily made, once it is suspected.

SUMMARY

Two cases of sickle cell anemia complicating pregnancy are presented and discussed. It is most likely that pregnancy is a factor in producing an exacerbation of the disease. The multiple thromboses which are often characteristic of the disease proved fatal in the second case. With proper supervision it is possible, however, to carry pregnancy successfully to term in spite of severe sickle cell anemia.

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STUDIES ON PREGNANDIOL*

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PREGNANDIOL is the only known excretion product of the corpus luteum hormone, progesterone, in the urine. In this study the pregnandiol content of the urine was determined in 5 cases in which the menstrual history was normal, in 50 cases in which biopsy was performed on the endometrium of nongravid women who presented gynecologic complaints, in 10 cases of early gestation, in one case during the last month of gestation, and in 51 cases during the first week post partum. With the exception of the 5 normal nongravid women, all of these patients were seen in the Section on Obstetrics and Gynecology at the Mayo Clinic.

HISTORY OF PREGNANDIOL

Marrian, in 1929, made extracts from the urine of pregnant women for further chemical study of estrogenic compounds and obtained a physiologically inactive solid alcohol which he did not identify. Butenandt, in 1930, had also observed this inactive substance and, after the accumulation of nearly 2 gm. of the material from the residues remaining from the extraction of estrone from more than 1000 liters of

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urine of gravid women, was able to identify it. He named it "pregnandiol" because it was thought to occur only in the urine of pregnancy. The formula which Butenandt gave pregnandiol is $C_{21}H_{36}O_2$. The structural formula as proved by him is given in Fig. 1, *A*. Progesterone, the hormone of the corpus luteum, has the formula $C_{21}H_{30}O_2$[3]; its structural formula is shown in Fig. 1, *B*.

From a comparison of these two formulas, it is seen that the unsaturated diketone, progesterone, differs but little from the saturated alcohol, pregnandiol. Butenandt and Schmidt, in 1934, having noted this structural similarity, were able to produce pure progesterone from pregnandiol by a method of pseudosynthesis. By oxidizing pregnandiol obtained from the urine of pregnant women, they obtained a saturated diketone which was brominated and this product was treated with pyridine to effect the elimination of hydrogen bromide. The unsaturated diketone thus obtained was identical with the corpus luteum hormone, progesterone. The physiologic potency of progesterone obtained in this manner from pregnandiol has been proved by Selye and his collaborators in some of their work on the relationship between progesterone and estrin. Odell and Marrian made a further contribution when they found an acid-hydrolyzable form of pregnandiol in the alcohol-washed butyl alcohol extract obtained from the urine of pregnant women. Venning and Browne, in 1936, presented a gravimetric method of extracting the water-soluble complex, sodium pregnandiol glucuronate, from the urine of pregnant women. In 1937, Venning, Henry,

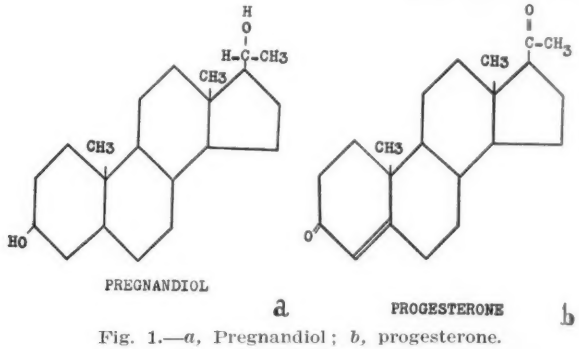


Fig. 1.—*a*, Pregnandiol; *b*, progesterone.

and Browne found this same complex in the urine of nongravid women and stated that it was present in significant amounts only during the luteal phase of the menstrual cycle. Because they found the substance excreted in increasing amounts throughout pregnancy, because of the close time relationship between the formation of the corpus luteum and the appearance of the complex in the urine during the menstrual cycle, and because intramuscular injection of progesterone was followed by the excretion of sodium pregnandiol glucuronate in the urine, they concluded that this last named compound was an actual excretion product of progesterone. There may be other compounds of progesterone excreted in the urine but pregnandiol is the only form now identified.

In the light of these findings, this relationship between the amount of pregnandiol in the urine and that of progesterone produced by the corpus luteum would seem to mean that the amount of pregnandiol in the urine would be an index to the function of the corpus luteum. It seems logical, therefore, to consider the determination of the pregnandiol content of the urine as a method for determining the function of the corpus luteum.

METHOD OF EXTRACTION

The butyl alcohol extraction method of Venning has been used in this study to determine the pregnandiol content of the urine. The butyl alcohol extract, obtained by this method, is evaporated to dryness and the residue is dissolved in 1/10 N

sodium hydroxide, which is then re-extracted with butyl alcohol and again evaporated to dryness. The residue is then dissolved in water and the sodium pregnandiol glucuronate in solution is precipitated two times with acetone. The precipitate obtained is dissolved in ethyl alcohol and, after the alcohol is evaporated, the residue, sodium pregnandiol glucuronate, is weighed.

The complex extracted directly from the urine is a monosodium salt of pregnandiol glucuronic acid. The formula for this salt is $C_{27}H_{43}O_8$-NaH_2O. It contains one molecule of water of crystallization and has a molecular weight of 536. Since the molecular weight of pregnandiol is 320, the factor for conversion of sodium pregnandiol glucuronate into terms of pregnandiol is 320/536 or 0.597. The values stated in this paper are in terms of pregnandiol.

In the determination of the pregnandiol content of the urine after the method of Venning, considerable care is exercised in the removal of impurities by dissolving the residue in water and precipitating the sodium pregnandiol glucuronate with acetone; this is followed by centrifugation and filtration. There may be, however, a small amount of impurity present in the final product which varies directly with the amount of urine extracted and inversely with the amount of pregnandiol present; for example, a relatively small volume of urine containing a relatively large amount of pregnandiol will yield a nearly pure product, whereas a large volume of urine containing a small amount of pregnandiol will give a product which is for the most part impure. In cases in which the final weight of the sodium pregnandiol glucuronate is of the order of 0.5 mg. or less, we consider that the residue consists mainly of extraneous substances and that the amount of sodium pregnandiol glucuronate is negligible.

OTHER METHODS OF EVALUATING CORPUS LUTEUM FUNCTION

Until the aforementioned method for estimating the amount of pregnandiol in the urine was developed, the principal measure of function of the corpus luteum was the microscopic appearance of differentiative changes in the endometrium. Infertility, menorrhagia, metrorrhagia, a shortened interval between the menstrual periods, repeated abortions, and perhaps dysmenorrhea, often suggested a deficient or absent function of the corpus luteum. It is not within the scope of this paper, however, to discuss the differences of opinion in regard to the etiology, terminology, and significance of the changes that may occur in the endometrium as a result of disturbance in normal hormonal stimulation. The terminology of Herrell and Broders has been employed to classify normal and abnormal endometriums: The terms "early" and "late proliferation" are given by them to the early and late effect of estrin on the endometrium in the first half of the menstrual cycle (Fig. 2). "Early" and "late differentiation" are the terms they applied to the early and late effect of progesterone on the endometrium in the luteal phase or last half of the menstrual cycle (Fig. 3).

The microscopic findings in the endometrium that seem to indicate disturbance of the progesterone effect are degrees of failure of development of differentiation. The differentiative phase in the endometrium is often designated as the "secretory phase." Cystic degeneration is often associated with this evidence of failure and, in its most marked form, has been called "cystic glandular hyperplasia." Failure of progesterone to stimulate the endometrium normally results in degrees of lack of differentiation that often seem to be in proportion to the symptoms that the patient presents. By microscopic study of these endo-

metriums, one of us[7] has shown that cystic changes can occur in all phases of the menstrual cycle. Thus, cystic changes in a differentiated endometrium probably are the first microscopic evidence of functional failure of the corpus luteum (Fig. 4). Complete absence of differentiation, with persistence of proliferation with or without cystic change

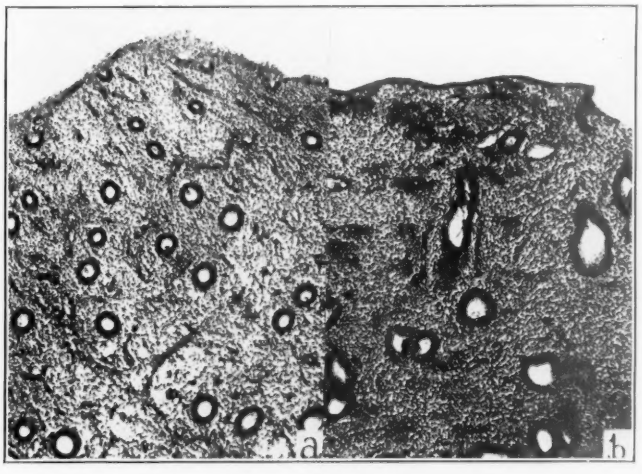


Fig. 2.—*A* (Case 1, Table I.), Early proliferative phase of the menstrual cycle in a normal endometrium (hematoxylin and eosin, ×50); B (Case 4, Table I.), late proliferative phase of the menstrual cycle in a normal endometrium (hematoxylin and eosin, ×50).

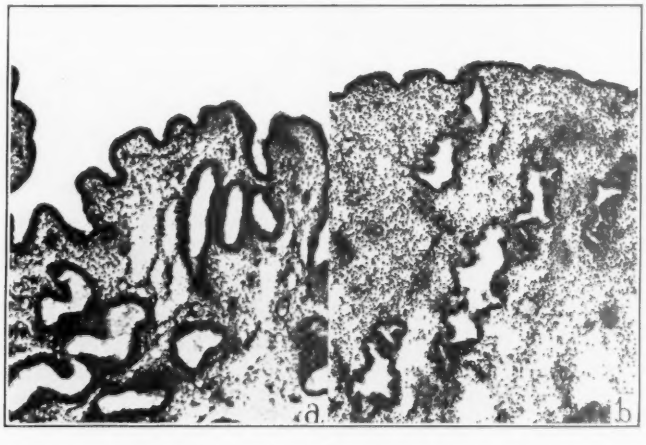


Fig. 3.—*A* (Case 10, Table I.), Early differentiative phase of the menstrual cycle in a normal endometrium (hematoxylin and eosin, ×50); *B* (Case 17, Table I.), late differentiative phase of the menstrual cycle in a normal endometrium (hematoxylin and eosin, ×50).

(Figs. 5 and 6, *A*), apparently is associated with complete absence of function of the corpus luteum, although it indicates that estrogenic stimulation is still present. When this state exists, the diagnosis of persistent proliferation of the endometrium is made. Complete failure of the ovary to produce estrin naturally results in atrophy of the endometrium (Fig. 6, *B*). This series of cases in which endometrial biopsy

was performed did not happen to reveal an endometrium in the stage of early proliferation in association with cystic change. A slide of endometrial tissue showing this type of microscopic change was therefore borrowed from the Section on Surgical Pathology in order to make the series of photomicrographs more representative (Fig. 5, *A*).

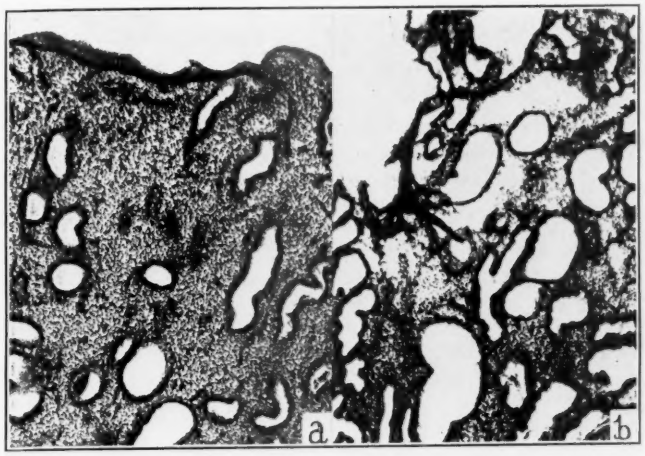


Fig. 4.—*A* (Case 49, Table III.), Early differentiative phase of the menstrual cycle in an endometrium with cystic changes Grade 2 (hematoxylin and eosin, ×50); *B* (Case 44, Table III.), late differentiative phase of the menstrual cycle in an endometrium with cystic changes of Grade 4 (hematoxylin and eosin, ×50).

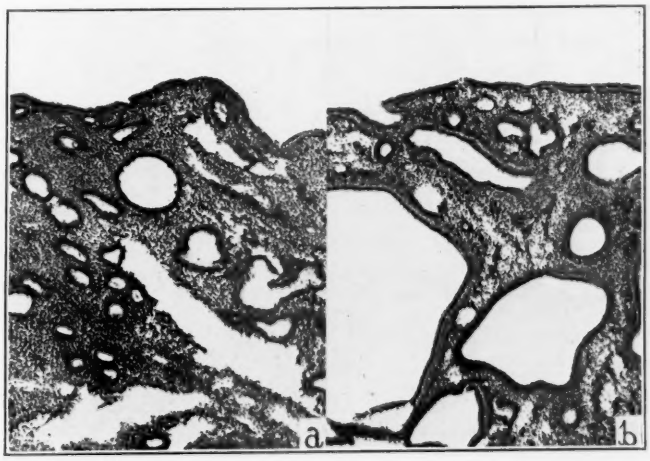


Fig. 5.—*A*, Early proliferative phase of the menstrual cycle in an endometrium with cystic changes of Grade 2 (hematoxylin and eosin, ×50); *B* (Case 27, Table II.), late proliferative phase of the menstrual cycle in an endometrium with cystic changes of Grade 4 (hematoxylin and eosin, ×50).

NORMAL VALUES FOR PREGNANDIOL IN THE URINE

No great amount of data is as yet available in regard to the amounts of pregnandiol to be found in the urine of nongravid women with normal genital function. Venning and Browne[12] presented the results of

pregnandiol determinations in 10 cases in which the menstrual history was normal. These determinations were not controlled by microscopic study of the endometrium. The basis for acceptance of Venning's values as normal is therefore the menstrual history. It is a well-known fact, however, that the menstrual history is often inaccurate. Furthermore, cases are often encountered in which cyclic uterine bleeding occurs from an undifferentiated endometrium, bleeding indistinguishable clinically from normal menstruation. Values for pregnandiol obtained in cases in which the only basis for normalcy is the occurrence of uterine bleeding at regular intervals therefore may be open to question. Thus in the cases reported by Venning, pregnandiol was found only for a period of three days in the luteal phase in one case and, in other cases, it was present for a period of twelve days. On the days of the luteal phase of the menstrual cycle when pregnandiol was found in the urine of all of Venning's patients the values varied from 1 to 7.2 mg. in twenty-four hours.

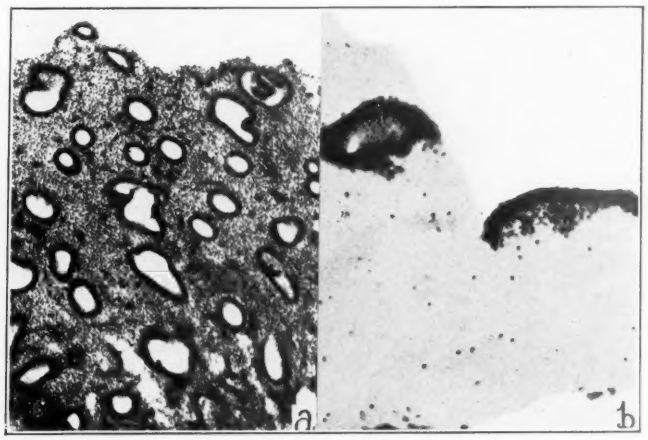


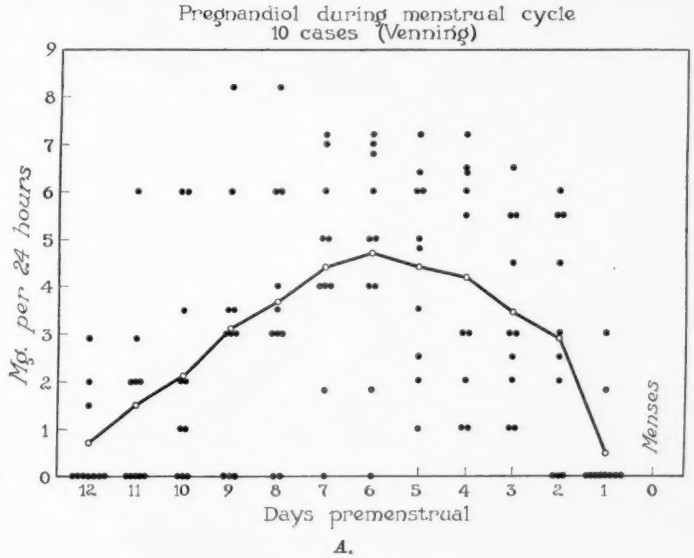
Fig. 6.—*A* (Case 24, Table II.), Early and late proliferative phases of the menstrual cycle in an endometrium with cystic changes of Grade 2 (hematoxylin and eosin, ×50); *B* (Case 22, Table II.), atrophic endometrium (hematoxylin and eosin, ×110).

Perhaps microscopic study would have revealed abnormal endometriums in some of these cases.

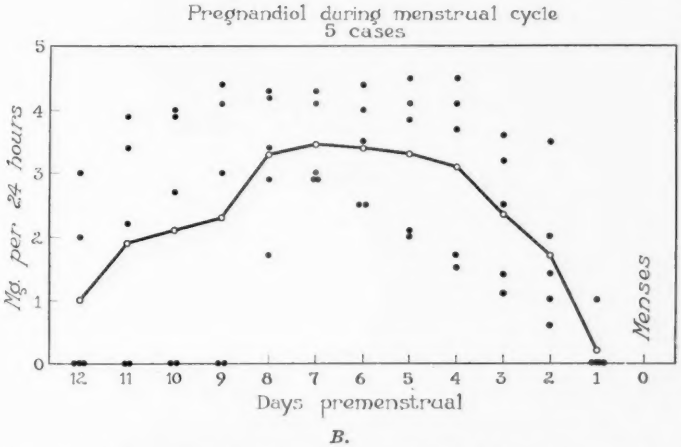
For these reasons it is not possible to state definitely the range of normal excretion of pregnandiol and such data as are available at this time are merely indicated. Fig. 7, *A* is a composite curve for the excretion of pregnandiol which has been constructed by us from the values reported by Venning. Fig. 7, *B* represents the same type of curve for a group of apparently normal women whose excretion of pregnandiol was measured by us.

In the human subject it is customary to consider the menstrual cycle as extending from the first day of a period to the first day of the succeeding period. It will be noted in Fig. 7 that the luteal phase of the menstrual cycles was found by counting back from a menstrual period rather than by counting forward from the first day of the preceding menstrual period. This was done for the reason that, if a menstrual period has

occurred in a normal individual, more definite dates can be assigned to the luteal phase than if the time of the luteal phase is based on the occurrence of an anticipated menstrual period. Repeated microscopic studies of the endometrium of several hundred normal women during the luteal phase of the menstrual cycle will have to be studied, together with the results of repeated estimations of pregnandiol for the same



A.



B.

Fig. 7.—Excretion of pregnandiol: *A*, Graph constructed from Venning's report; *B*, graph constructed from our observations.

patients, in order to solve the problem of normal values. Until such a time as this can be accomplished, the values given in Fig. 7 will have to suffice as the criteria of normal excretion of pregnandiol in the urine.

The estimations thus far made by us of the amounts of pregnandiol in the urine of presumably normal women during the luteal phase of the menstrual cycle correspond to those of Venning.

RESULTS

I. Cases in Which Pregnandiol Was Estimated and in Which Endometrial Biopsy Was Performed.—The data which were obtained from an investigation of the 50 cases in which endometrial biopsy was performed are shown in Tables I, II and III. Table I reveals the amounts of pregnandiol present in cases in which the endometrium was normal microscopically. It is to be emphasized that these patients presented

TABLE I. CASES IN WHICH PREGNANDIOL WAS DETERMINED AND IN WHICH ENDOMETRIAL BIOPSY REVEALED A NORMAL MICROSCOPIC APPEARANCE OF THE ENDOMETRIUM

CASE	DAYS BEFORE AND AFTER ONSET OF MENSES	AMOUNT OF PREGNANDIOL PER 24 HR., MG.	REPORT OF ENDOMETRIAL BIOPSY, PHASE	COMPLAINTS AND OTHER DATA
1*	No cycle	1.28	Early proliferative	Scanty flow every few days for past year
2	15 after 13 before	0.557	Early proliferative	Infertility, scanty menses. Nonpatent tubes
3	20 after ? before	0.51	Late proliferative	Sterility and obesity. Past 2 years menses irregular and scanty. Last interval 3 mo.
4*	10 after 18 before	0.342	Late proliferative	Infertility. Dysmenorrhea. Flow lasts from 5 to 14 days
5	11 after 17 before	0.55	Late proliferative	Infertility. Tubes patent. Basal metabolic rate -13 and -15
6	13 after 22 before	1.48	Late proliferative	Infertility
7	21 after 0-8 before	0.855	Late proliferative	Secondary infertility. Tubes patent. Obesity
8	19 after 11-21 before	0.34	Late proliferative	Infertility. Menstrual interval 30-40 days, flow 9 days. Tubes patent. Husband negative. Basal metabolic rate -21 and -10
9	17 after 11 before	2.9	Early differentiative	Menorrhagia, 1 year. Serologic tests for syphilis, 4+
10*	20 after 3-9 before	9.85	Early differentiative	Infertility. Husband sterile
11	22 after 6 before	0.342	Early differentiative	Infertility. Previous right tubal pregnancy. Tubes nonpatent
12	25 after 3 before	5.9	Late differentiative	Mild dysmenorrhea. Urinary prolan: 20 R.U./liter; urinary estrin: 40 + R.U./liter; (12th day of cycle)
13	24 after 4 before	0.457	Late differentiative	Infertility. Basal metabolic rate low for 7 years
14	24 after 3 before	5.6	Late differentiative	Infertility, 3 years. Menorrhagia, 5 years. Basal metabolic rate -12
15	24 after 4-6 before	0.6	Late differentiative	Infertility, 7 years. Tubes patent. Basal metabolic rate -4
16	28 after 0-1 before	0.26	Late differentiative	Infertility. Basal metabolic rate -12
17*	23 after 5 before	0.3	Late differentiative	Secondary infertility. Very scanty menses, lasting only 2 days. Basal metabolic rate 0. Tubes nonpatent to inflation and iodized oil

*Photomicrographs of the endometriums in these cases shown in Figs. 2 and 3.

histories of the complaints previously mentioned which are considered to be evidence of disturbance in normal genital function even though microscopic examination of the endometriums revealed no abnormality. Significant amounts of pregnandiol were present in two (Cases 1 and 6) of the 8 cases in which the endometrium was in the proliferative phase. Case 1 was one of metrorrhagia in which persistent proliferation existed. In Case 6, the significant amount of pregnandiol was found in conjunction with the late proliferative phase.

In the remaining 9 cases in this table, the endometrium was in a stage of differentiation. In 4 of these 9 cases amounts of pregnandiol were present which might be considered as normal in light of the values obtained in cases in which the menstrual cycle is normal. Failure to find normal amounts of pregnandiol in conjunction with the microscopically normal endometriums in the other five cases demands some explanation. In Case 16, it is to be noted that the determination of pregnandiol and the biopsy were made the day before the onset of the menstrual

TABLE II. CASES IN WHICH PREGNANDIOL WAS DETERMINED AND IN WHICH ENDOMETRIAL BIOPSY REVEALED AN ABNORMAL PROLIFERATED ENDOMETRIUM

CASE	DAYS BEFORE AND AFTER ONSET OF MENSES	AMOUNT OF PREGNANDIOL PER 24 HR., MG.	REPORT OF ENDOMETRIAL BIOPSY, PHASE	COMPLAINTS AND OTHER DATA
18	60 after ? before	1.11	Late proliferative, Grade 2, cystic	Metrorrhagia, 3 months. Infertility, husband sterile. Obesity. Basal metabolic rate +1
19	No cycle	0.0	Late proliferative, Grade 2, cystic	Metrorrhagia, 1 to 6 napkins required daily for past 4 years
20	24 after 4 before	0.42	Late proliferative, Grade 2, cystic	Age 40, "normal" menses, 5 normal pregnancies. No gynecologic complaints
21	20 after 2-15 before	1.28	Late proliferative, Grade 1, cystic	Habitual abortion. Irregular cycle, interval 22 to 35 days
22*	No cycle	0.426	Atrophic endometrium	Nervousness, nausea, vomiting, relieved by menstruation, 4 years' amenorrhea, age 16 to 20, now age 26. Periods now about every 4 months. Basal metabolic rate -22. Urinary estrin: +10 R.U./24 hours. Prolan: 0
23	14 after 3 before	0.486	Late proliferative, Grade 2, cystic	Migraine. Short 17-day cycle with 7-day flow. Basal metabolic rate -7
24*	20 after 12 before	0.342	Early and late proliferative, Grade 2, cystic	7 abortions from 1921 to 1937. Obesity and headaches. Basal metabolic rate +9
25	15 after 13 before	0.298	Late proliferative, Grade 2, cystic	Infertility, 2 years. Appendicitis and peritonitis 6 years ago. Tubes patent. Husband: 0. Basal metabolic rate -11 and -8
26	No cycle	0.47	Late proliferative, Grade 1, cystic	Menometrorrhagia, otitis media. Basal metabolic rate +52, +39, +47, +30
27*	No cycle	0.94	Late proliferative, Grade 4, cystic	Menometrorrhagia
28	No cycle	1.71	Late proliferative, Grade 2, cystic	Menometrorrhagia

*Photomicrographs of the endometriums in these cases are shown in Figs. 5 and 6.

TABLE III. CASES IN WHICH PREGNANDIOL WAS DETERMINED AND IN WHICH ENDOMETRIAL BIOPSY REVEALED AN ABNORMAL DIFFERENTIATED ENDOMETRIUM

CASE	DAYS BEFORE AND AFTER ONSET OF MENSES	AMOUNT OF PREGNANDIOL PER 24 HR., MG.	REPORT OF ENDOMETRIAL BIOPSY, PHASE	COMPLAINTS AND OTHER DATA
29	27 after 2 before	1.11	Late differentiative, Grade 3, cystic	Infertility, 5 years. Spontaneous abortion 7 years ago
30	17 after 9 before	1.79	Early differentiative, Grade 2, cystic	Sterility, obesity, arthritis. Basal metabolic rate +1
31	25 after 3 before	0.597	Early differentiative, Grade 3, cystic	Two episodes of vaginal spotting
32	20 after 8 before	2.8	Early differentiative, Grade 2, cystic	Infertility, 4 years. Husband: -0. Tubes patent
33	19 after 8 before	3.8	Early and late differentiative	Infertility. Tubes patent. Basal metabolic rate +3. Urinary prolan: 0 Estrin: 21 R.U./24 hr.
34	19 after 11 before	5.0	Early differentiative, Grade 2, cystic	Infertility. Tubes patent. Basal metabolic rate -17, -8
35	22 after 2 before	0.254	Late differentiative, Grade 1, cystic	Secondary infertility, 1½ years. Has one child age 3. Basal metabolic rate -2
36	34 after ? before	0.076	Late proliferative and early differentiative	Regular menses until 1 year ago. Since every 42 to 49 days, scanty. Hirsutism, obesity, dysmenorrhea. Basal metabolic rate -2. Urinary estrin: 20 R.U./24 hr.
37	24 after 6-11 before	2.9	Late differentiative, Grade 4, cystic	Infertility. Tubes nonpatent to 200 mm. Hg.
38	16 after 14 before	0.85	Early differentiative, Grade 1, cystic	Occasional vaginal spotting. Infertility. Chronic mastitis. Basal metabolic rate: 0
39	24 after 4 before	2.39	Late differentiative, Grade 2, cystic	Infertility, 3 years. Mittelschmerz. Tubes patent. Basal metabolic rate -16, -25, -22
40	20 after 6 before	0.5	Late differentiative, Grade 2, cystic	Infertility, 4 years. Tubes patent. Husband had reduced number sperm. Basal metabolic rate -4
41	23 after 5 before	4.0	Early and late differentiative, Grade 2, cystic	Recurrent pyelonephritis, colon bacilluria, trichomonas, sterility (husband sterile). Basal metabolic rate -9
42	21 after 7 before	0.34	Late differentiative, Grade 2, cystic	Infertility. Tubes patent. Basal metabolic rate -11
43	22 after 6 before	1.37	Late differentiative, Grade 1, cystic	Infertility, 7 years. Husband: 0. Tubes patent
44*	27 after 2 before	1.62	Late differentiative, Grade 4, cystic	Dysmenorrhea. Trichomonas. Basal metabolic rate -11, -8

*Photomicrographs of the endometriums in these cases are shown in Fig. 4.

TABLE III—CONT'D

CASE	DAYS BEFORE AND AFTER ONSET OF MENSES	AMOUNT OF PREGNANDIOL PER 24 HR., MG.	REPORT OF ENDOMETRIAL BIOPSY, PHASE	COMPLAINTS AND OTHER DATA
45	24 after 4 before	1.78	Late differentiative, Grade 2, cystic and polypoid	Secondary infertility. 2 normal preg., 6 and 7 years ago. Tubes patent. Basal metabolic rate -7
46	22 after 6 before	0.256	Late differentiative, Grade 1, cystic	Mild dysmenorrhea
47	18 after 10 before	0.65	Late differentiative, Grade 2, cystic	Infertility, 6 years. Tubes patent. Husband: 0. Basal metabolic rate +11
48	25 after 3 before	1.2	Late differentiative, Grade 1, cystic	Trichomonas. Chronic cystic mastitis
49*	18 after 3 before	0.513	Early differentiative, Grade 2, cystic	Oligomenorrhea. Secondary infertility 4 yr. Tubes patent. Basal metabolic rate +15, +21, +18, -11
50	21 after ? before	0.94	Early differentiative, Grade 1, cystic	Menorrhagia, irregular interval, infertility. Tubes patent. Basal metabolic rate +2

*Photomicrographs of the endometriums in these cases are shown in Fig. 4.

flow. In the present state of our knowledge, it is considered that the amount of progesterone secreted by the corpus luteum is markedly less just before the onset of menstruation, therefore one would expect pregnandiol to be absent or to be present in only minimal amounts in the urine at this stage of the cycle. In the other cases of this type, it is entirely possible that the determinations were made too close to the time of the menstrual period because of an inaccurate menstrual history; it is quite common for a woman to be inaccurate, to the extent of four or five days, in giving her menstrual history. It may be that these cases might have shown a normal excretion of pregnandiol had the opportunity for several estimations been available. During the course of this investigation, it has become increasingly evident that the amounts of progesterone (as evidenced by the excretion of pregnandiol in the urine) which are necessary to differentiate the endometrium in a given case may vary considerably. For example, in the 5 cases under discussion, in which low values for pregnandiol were associated with a normally differentiated endometrium, it may be that these endometriums differentiated in response to a minimal amount of progesterone.

This theory of endometrial response, while in no way conclusive, may have some practical significance. Here are 5 cases in which the endometrium was normal microscopically and yet infertility and scanty menses were complained of. Heretofore, these cases might have been considered normal from the hormonal standpoint, but this low finding of urinary pregnandiol may indicate that there is a deficiency of the corpus luteum in this type of case.

Table II shows the amounts of pregnandiol present in 11 cases in which, with one exception, the endometrium was in a stage of proliferation. In this one exception (Case 22), microscopic examination revealed an atrophic endometrium. In 8 of these cases minimal amounts of pregnandiol were present, which is the expected finding during the proliferative phase; however, it is significant that in Cases 18, 21, and 28, more than 1 mg. of pregnandiol was found in a twenty-four-hour specimen of urine. It is to be noted that this finding occurred in association with the late proliferative phase. In six of these 11 cases (Cases 18, 19, 23, 26, 27, and 28), the fact that the patients bled from a proliferated endometrium would indicate a

persistence of proliferation and probably a complete or nearly complete failure of the corpus luteum. Case 20 is of interest because it is illustrative of the findings in women approaching the menopause, and it also illustrates the fact that cyclic uterine bleeding can occur from a proliferated endometrium.

The data obtained in the remaining 22 of the 50 cases in this group are given in Table III. In these cases, the endometrium was in a stage of differentiation. In 12 of these 22 cases, significant amounts of pregnandiol were found in the urine, and, in 3 (Cases 33, 34 and 41) of these 12, amounts of pregnandiol were present which were in the upper normal range.

It is evident, from the data presented in Table III, that in only 3 of these 22 cases were normal or maximal amounts of pregnandiol found. It is to be noted that in 20 of the 22 cases in this table a significant amount of cystic change was found in the differentiated endometrium; this indicates to us that these were not normal endometriums.

It was possible to make repeated estimations of the urinary pregnandiol in Cases 34 and 35, during a considerable part of the menstrual cycle. The data collected in these two cases again emphasize the value of repeated estimations of pregnandiol. The amounts of pregnandiol per twenty-four hours and the time in the cycle during which these amounts were obtained is shown in Table IV. Both of these patients had regular menstrual cycles and a flow which did not vary from normal in amount or duration. In Case 34, menstruation occurred every thirty days and lasted five days; in Case 35, menstruation occurred every twenty-four days and lasted three days. From the standpoint of the menstrual history these patients might well be considered as normal, and such cases as these might occur in any group such as those studied by Venning and by us for normal excretion of pregnandiol. Because of the cystic changes in the endometrium which were evident microscopically, however, it would seem that these patients were not normal. This, therefore, serves again to emphasize the statement previously made that the menstrual history is not necessarily an accurate criterion of normalcy. If endometrial biopsy had not been performed in these two cases, Case 34 might well have been considered normal because the amounts of pregnandiol that were excreted in the urine were in the range of normal values. On the other hand, Case 35 would have been considered abnormal because of the small amounts of urinary pregnandiol that were found. Examination of the endometrium revealed that Case 34, which had the greatest corpus luteum function as evidenced by urinary pregnandiol, showed a more marked

TABLE IV. AMOUNT OF PREGNANDIOL PER TWENTY-FOUR HOURS

AMOUNT OF PRENANDIOL PER 24 HR., MG.	DATE IN CYCLE
Case 34 (30-Day Cycle)	
0.8	11
0.51	13
2.6	14
6.2	15
4.0	16
3.2	18
5.0	19*
Case 35 (24-Day Cycle)	
0.597	15
0.51	16
0.68	17
0.43	18
0.21	19
2.6	20
0.254	22†
0.34	23
0.34	24

*Biopsy revealed early differentiation, Grade 2 cystic endometrium.
†Biopsy revealed late differentiation, Grade 1 cystic endometrium.

degree of cystic change in the endometrium than did Case 35 in which a higher degree of cystic change would have been expected. It would seem that a logical explanation for these findings, as has been previously indicated, is that the endometrium must be considered as a definite entity and that the endometrial response to progesterone is a variable factor.

It may ultimately be shown that normal hormonal function is more dependent on the relation between the amounts of estrogenic hormone and progesterone than upon the actual amounts of either. It is well known that the corpus luteum does produce estrogenic hormone as well as progesterone. It is logical to infer that the estrogenic hormone secreted by the corpus luteum is essential to the development and function of the endometrium during the luteal phase of the menstrual cycle.

It seems evident, therefore, from the data in these two cases, that an evaluation of the function of the corpus luteum is much more accurate when several determinations of pregnandiol can be made and that normal values for pregnandiol and a normal menstrual history may be entirely misleading unless endometrial biopsy is performed.

II. Estimation of Pregnandiol in the Urine of Gravid Women.—The data obtained from estimations of pregnandiol in 10 cases during early gestation are shown in Table V. In all these cases the history was of normal, regular menstruation, one or two periods had been missed, and pregnancy was then later proved to be present. It is evident that pregnandiol was excreted in the urine in all of these cases either in normal amounts or in amounts in excess of those found during the luteal phase of the menstrual cycle. The data on urinary pregnandiol during gestation are incomplete, but the amounts found during the later months of gestation are considerably

TABLE V. CASES IN WHICH DETERMINATIONS OF PREGNANDIOL WERE MADE DURING EARLY GESTATION

CASE 2	DURATION OF GESTATION	AMOUNT OF PREGNANDIOL PER 24 HR., MG.
1	2 months	5.9
2	8½ weeks	14.4
3	6½ weeks	9.0
4	7 weeks	5.1
5	2 months	8.3
6	2 months	6.5
7	7½ weeks	10.11
8	3 months	4.7
9	6 weeks	4.9
10	2½ months	12.2

TABLE VI. RESULTS OF PREGNANDIOL DETERMINATIONS MADE DURING LAST MONTHS OF A NORMAL GESTATION

NUMBER OF DAYS BEFORE DELIVERY	AMOUNT OF PREGNANDIOL PER 24 HR., MG.
30	53.9
28	31.2
26	50.5
24	51.0
22	27.3
19	35.6
17	53.1
15	55.8
12	73.5
10	56.8
7	47.0
4	71.6
2	43.2

higher, varying between 27 and 75 mg. per twenty-four hours. Table VI shows the results obtained in one case in which pregnandiol estimations were made during the last month of normal gestation.

III. Estimation of Pregnandiol on the Fourth Day Post Partum.—The data obtained on estimating pregnandiol in 51 cases on the fourth day post partum are shown in Fig. 8. It is evident that in 45 and 21 per cent of these cases pregnandiol was excreted in negative and minimal amounts, respectively. In 16 per cent the urinary pregnandiol had a mean value of 2.75 mg. per twenty-four hours; in 18 per cent the mean value was 6.0 mg. per twenty-four hours.

COMMENT

It seems apparent from the data so far available that there is a considerable variation in the amount of pregnandiol excreted by women with a normal menstrual history, as well as a variation in the duration of excretion during the luteal phase of the menstrual cycle. The values obtained by Venning and by us for pregnandiol in the urine of women with a normal menstrual history are essentially the same.

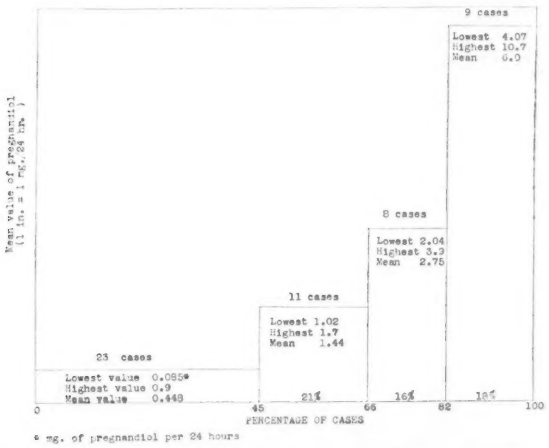


Fig. 8.—Excretion of pregnandiol on the fourth day post partum.

As is indicated in Tables I and II, significant amounts of pregnandiol have been found in the urine when a stage of proliferation existed in the endometrium. So far this has occurred, with but one exception, in association with the late proliferative phase of the endometrium. In this one exception persistent proliferation was present. This may be explained by the fact that there probably is an interval between the initial secretion of progesterone and the appearance of differentiation in the endometrium. It may be that in persistent proliferation of the endometrium some corpus luteum function is present, but not in a degree sufficient to cause endometrial differentiation. As Zondek has intimated, it may also be true that minimal amounts of progesterone continue to be produced by the corpus luteum of the preceding menstrual cycle.

The data obtained from studies carried out during the stage of endometrial differentiation, in which cystic changes were evident microscopically in 20 of 22 cases, reveal that definitely normal levels of preg-

nandiol were not present in the urine in 19 of the 22 cases. This would seem to mean that the low values obtained for pregnandiol indicated that normal function of the corpus luteum did not exist in these cases. It would seem logical, therefore, inasmuch as cystic changes have occurred in association with these low levels, that this finding can also be interpreted as evidence of insufficient function of the corpus luteum.

Low levels for pregnandiol occurred in five of the nine cases in Table I in which the endometriums were in the stage of differentiation and revealed no microscopic abnormality but in which some clinical abnormality was noted. This finding, and some of the findings in association with cystic degeneration during the stage of endometrial differentiation such as in Cases 33, 34, and 41 in Table III, would seem to indicate that the endometrial response to progesterone may vary considerably in different individuals. Furthermore these findings would seem to indicate that there may be some disturbance in the estrin-progesterone relationship. In addition, it seems evident that too much reliance should not be placed on the menstrual history as given by the patient, and it would also appear that a normal or abnormal excretion of pregnandiol in association with a normal menstrual history is not sufficient to evaluate accurately the hormonal status of any particular individual.

The data obtained from estimations of pregnandiol during early gestation would seem to mean that either normal amounts of urinary pregnandiol or amounts above normal in the case of a woman who has missed a menstrual period and whose menses have previously been regular is indicative of pregnancy. High amounts of urinary pregnandiol, such as were found in Cases 2, 7, and 10 in Table V, would seem definitely to indicate the presence of pregnancy. The excretion of pregnandiol in the remainder of these cases in amounts equal to or in excess of the upper limit of normal for pregnandiol excretion during the luteal phase of the menstrual cycle would seem to indicate pregnancy only if the fact of a missed menstrual period could be ascertained. In the last month of a normal gestation the amounts of pregnandiol in the urine in one case were found to be much greater and represented the highest excretion of pregnandiol so far observed by us.

As is indicated in Fig. 8, pregnandiol does not immediately disappear from the urine following parturition in a definite percentage of the cases, although the amount of urinary pregnandiol is much less than that found prior to parturition. This would seem to mean that there is some corpus luteum function after delivery. Whether or not this function is associated with lactation or some reparative process is not as yet known.

SUMMARY AND CONCLUSIONS

We have employed Venning's method for determining the amounts of pregnandiol in the urine, and in a group of cases comparable to those represented in her report the results of the test were essentially the same.

Pregnandiol was found in significant amounts in the urine during the luteal phase of the menstrual cycle in a majority of the cases studied.

Significant amounts of pregnandiol in the urine have been found during the stage of estrogenic activity when late proliferation existed in the endometrium.

An abnormal microscopic appearance of the differentiated endometrium is nearly always associated with low values for urinary pregnandiol. The endometrial response to apparently normal hormonal stimulation may vary.

Significant corpus luteum function, as evidenced by the amount of pregnandiol found in the urine, seems to be present on the fourth day post partum in about 50 per cent of the cases studied.

The excretion of pregnandiol in normal or maximal amounts in the urine of a woman who has missed a period and who has had a normal menstrual history is apparently indicative of early gestation.

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Kehrer, E.: Mongolism, Monatschr. f. Geburtsh. u. Gynäk. **108**: 125, 1938.

The author reports four cases of Mongolian idiocy and one rare case of familial Mongolism in which a father, his illegitimate sister and two daughters showed this disease. The cerebral disturbances associated with this abnormality may be so obvious at birth that a diagnosis can easily be made. The characteristic symptoms are the facial appearance, muscular hypotonicity, extremely lax skin in the back of the neck, tendency to remain inactive, drowsiness, and shortness and inward curvatures of the end phalanges of the five fingers.

Endocrine disturbances usually manifest themselves in the first few years of life but may be observed at birth. It is usually believed that Mongolian idiots appear in women after 40 years of age but only one of the author's four mothers was over 40.

The ultimate cause of Mongolism is to be sought partly in injury to the germ plasm (ovum or sperm) and partly to damage to the embryo early in its development.

J. P. GREENHILL.

X-RAY DEMONSTRATION OF SUBMUCOUS MYOMAS BY COMBINED USE OF HIPPURAN AND CO_2 INJECTION*

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INTRAUTERINE injection of radio-opaque solutions for the specific purpose of demonstrating submucous myomas began with collargol in 1914.† Since then other forms of colloidal silver and halogen salts have been employed. These have eventually been supplanted by iodized oils and at present lipiodol is most commonly preferred.

Two techniques are in vogue. One is the fractional and the other the evacuation method. The first consists of introducing 2 c.c. of lipiodol and making the x-ray exposure. This is followed by 4 or 5 successive films each after 4, 6, 8, and 10 c.c. have been introduced into the uterine cavity. The second method consists of filming the filled uterus at its maximum capacity and again as soon as the lipiodol has been evacuated.

Each of these methods gives telltale pictures in a certain percentage of cases, visualizing submucous myomas and other growths which protrude into the uterine cavity. Both have the disadvantage of allowing the oil to pass through the Fallopian tubes and of entering the peritoneal cavity. This drawback may to a certain extent be avoided by controlling the injection with the fluoroscope. The injection is discontinued the moment the uterine cavity is seen to be filled or the oil is seen entering the tubes. The fractional method necessitates multiple exposures which must be considered in relation to the examiner and the patient.

I have sought to avoid the escape into the peritoneal cavity by introducing into the uterus a thin rubber balloon (condom or Penrose tubing), coated with lipiodol on its outer and inner surfaces. Air injected into the balloon served as contrast. Unfortunately the inflated balloon does not adapt itself to the configuration of the uterine cavity, being limited largely by its molded form. Another device which I tried was to introduce a gelatin capsule containing ether after the lipiodol was evacuated, the expanding ether vapor liberated from the dissolved capsule serving to distend the uterine cavity. Neither of these methods has been found satisfactory. The introduction of a foreign body in addition to the lipiodol is not practical, occasioning, as it does, added trauma. Although the diagnosis of submucous myomas is important in selected cases, the method employed must be considered in relation to its safety, feasibility and simplicity.

*These illustrations were demonstrated at the scientific exhibit at the meeting of the American Gynecological Society, at Asheville, N. C., May 30, 1938.

In this work I had the valuable assistance of my Resident, Dr. Arthur H. Davids, who made the routine injections.

†Röntgendiagnostik der Uterustumoren mit Hilfe von intrauterinen Collargolinjektionen, Zentralbl. f. Gynäk., No. 18, 1914.

These conditions appear to be met by adopting the group of organic iodides such as uroselectan, skiodan, diodrast and hippuran, which have been utilized in excretory urography. They have the virtue of rapid absorption. They are nonirritant and are well tolerated by the blood stream. Their elimination by the kidneys is rapid and unaccompanied or followed by harmful lesions.

For intrauterine use the amount of the organic iodide employed is not enough as a rule to visualize the urinary tract. The solution may, however, when the Fallopian tubes are freely patent enter the peritoneal cavity from which it is rapidly resorbed and soon appears in the kidney pelves, ureters, and bladder. As this occurs well after the uterographs have been obtained, they offer no confusion.

Of the substances mentioned, hippuran has so far been used for our present purposes although it is quite possible that the others may yield equally good results. It is available in crystalline powder and can be made up into 100 per cent solution, in which state it can be kept at a moderately warm temperature. When cooled it crystallizes, requiring heating before the injection. In this saturation it remains a clear solution for a half hour or somewhat longer. Weaker solutions were first used and although shadowgraphs were obtained they were not as satisfactory as the 100 per cent solution (1 gm. of hippuran to 1 c.c. of distilled water).

The hippuran is introduced into the uterine cavity by means of a 20 c.c. syringe and uterine cannula, both of which are kept warm. An x-ray exposure is made at the point when the uterine cavity is filled. As a rule, from 5 to 10 or 15 c.c. are needed in fibromyomatous uteri under pressures varying between 40 mm. Hg and 150 mm. Hg.

After the x-ray exposure is made the hippuran is withdrawn into the syringe and the cannula is removed. It is well to allow two or three minutes for the uterus to empty itself. The solution is aspirated and whatever amount remains is expelled. Another syringe filled with 20 c.c. CO_2 is now attached to a clean cannula, 1 or 2 c.c. being discharged into sterile fluid in order to displace the air contained in the uterine cannula. The cannula is introduced into the uterine cavity and the CO_2 is injected until a sense of resistance is reached which is similar to that experienced during the injection of hippuran. At this point an x-ray exposure is made. (A bullet forceps grasps the anterior cervix lip and the cannula is introduced so that its tip is just above the internal os, the rubber or metal acorn engaging the external os to prevent regurgitation.)

A manometer, indispensable when lipiodol is used, is not required with hippuran. I have first insufflated the uterus with CO_2 in order to determine the initial pressure rise necessary to force the CO_2 through the uterotubal junction, using this pressure as a guide in injecting the solution. The latter was also injected by the graduated force of the CO_2 delivered from an insufflation apparatus both for the practical control of the pressure as well as to observe differences in pressure between

the fluid and CO_2. In this maneuver it is only necessary to hold the graduated glass tube containing the radio-opaque fluid above the level of the body.

It was found that the pressures reached by the aqueous solutions exceeded to some extent those reached by the CO_2. These were not as great as when lipiodol was used. Hence the manometer was found dispensable and in the last injections we have resorted to manual injection of hippuran depending upon the filling sensation imparted to the hand.

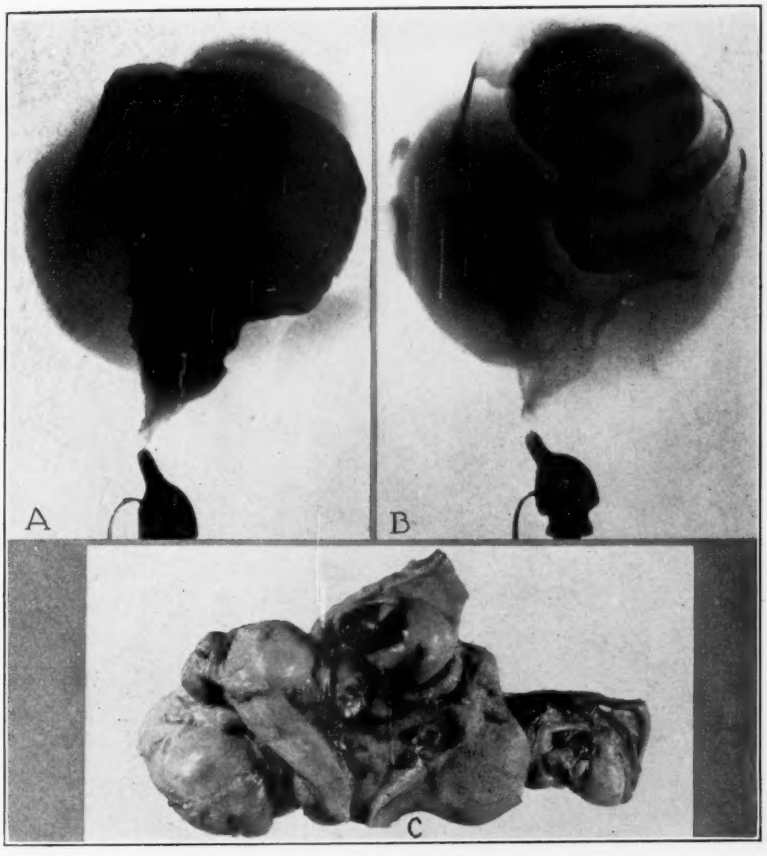


Fig. 1.—Case E. C. *A*, Hippuran hysterogram of specimen showing an irregular dilated cavity. No definite diagnosis of submucous fibroid can be made from this hysterogram. *B*, Hysteroaerogram with CO_2 injected after hippuran shows multiple submucous tumors as seen in the specimen, Fig. 1, *C*. *C*, Uterus cut open showing multiple submucous myomas visualized in Fig. 1, *B*.

RESULTS

The hippuran shadow by itself may not present the slightest indication of an intrauterine tumor. This may be seen in Fig. 1, *A*, Case E. C., where the hippuran hysterogram of the specimen showed an irregular cavity, the outline of submucous myomas definitely appearing in the hysterogram following the intrauterine injection of CO_2 (Fig. 1, *B*).

In Fig. 2, *A*, Case B. H., a single submucous myoma was not diagnosable by the hippuran hysterogram. It was beautifully outlined in the CO_2 contrast film (Fig. 2, *B*).

The same negative finding was seen in Fig. 3, *A*, Case M. M., where neither in the clinical hysterogram, by using hippuran 100 per cent nor in the specimen was a diagnosis possible of a submucous myoma (Fig. 3, *B*). The outline of the submucous tumor showed up definitely in the clinical hysterogram after CO_2 (Fig. 3, *B*), and it was also demonstrable in the specimen by the aid of CO_2 (Fig. 3, *D*).

Fig. 4, *A*, Case I. G., presents an irregular shadow with the hippuran, whereas the contrast afforded by CO_2 shows definite protrusion into the uterine cavity (Fig. 4, *B*). Uterus opened up showing the submucous myoma, *C*.

Fig. 5, *A*, Case S. K., shows no special deviation from the normal triangular shape of the uterine cavity by hippuran, whereas the submucous nature of the tumor is shown in the hysterogram with CO_2 (Fig. 5, *B*).

When a crescentic shadow is obtained by the hippuran alone, it is strongly presumptive evidence of a submucous myoma (Fig. 6, *A*). In such cases the contrast

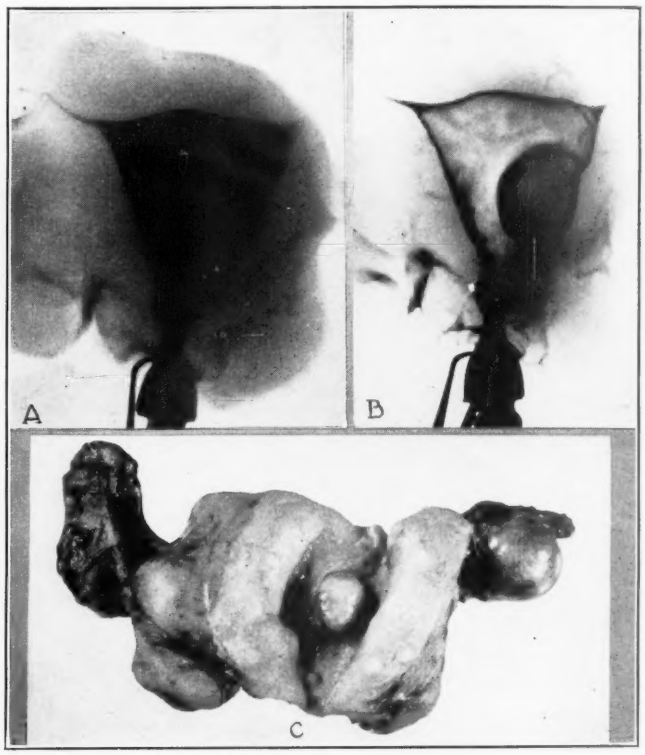


Fig. 2.—Case B. H. *A*, Hysterogram with hippuran 100 per cent solution shows a dilated uterine cavity but no marked suggestion of the presence of a submucous myoma. *B*, Hysteroaerogram with CO_2 injected after hippuran shows a solitary submucous fibroid which may be seen in Fig. 2, *C*. *C*, Uterus cut open showing a solitary submucous fibroid visualized in Fig. 2, *B*.

given by the CO_2 hysterogram is particularly striking, as can be seen in Fig. 6, *B*, Case P. B. In this case the submucous myoma was removed by abdominal myomectomy after which the hysterogram, Fig. 6, *C*, showed the return to the more or less triangular configuration of the uterine cavity (Fig. 6, *E*) and is prettily demonstrated in the CO_2 hysterogram, Fig. 6, *E*. Another illustration of the return to the triangular shape of the uterine cavity after a myomectomy is seen in Figs. 10, *A*, 10, *B*, 10, *C*, and 10, *D* (Case F. W.).

Fig. 7, *A*, Case C. S., illustrates a submucous myoma in the process of being extruded. The hysterogram with hippuran is not characteristic whereas the CO_2 hysterogram shows the lower pole of the tumor protruding into the cavity of the uterus near the internal os.

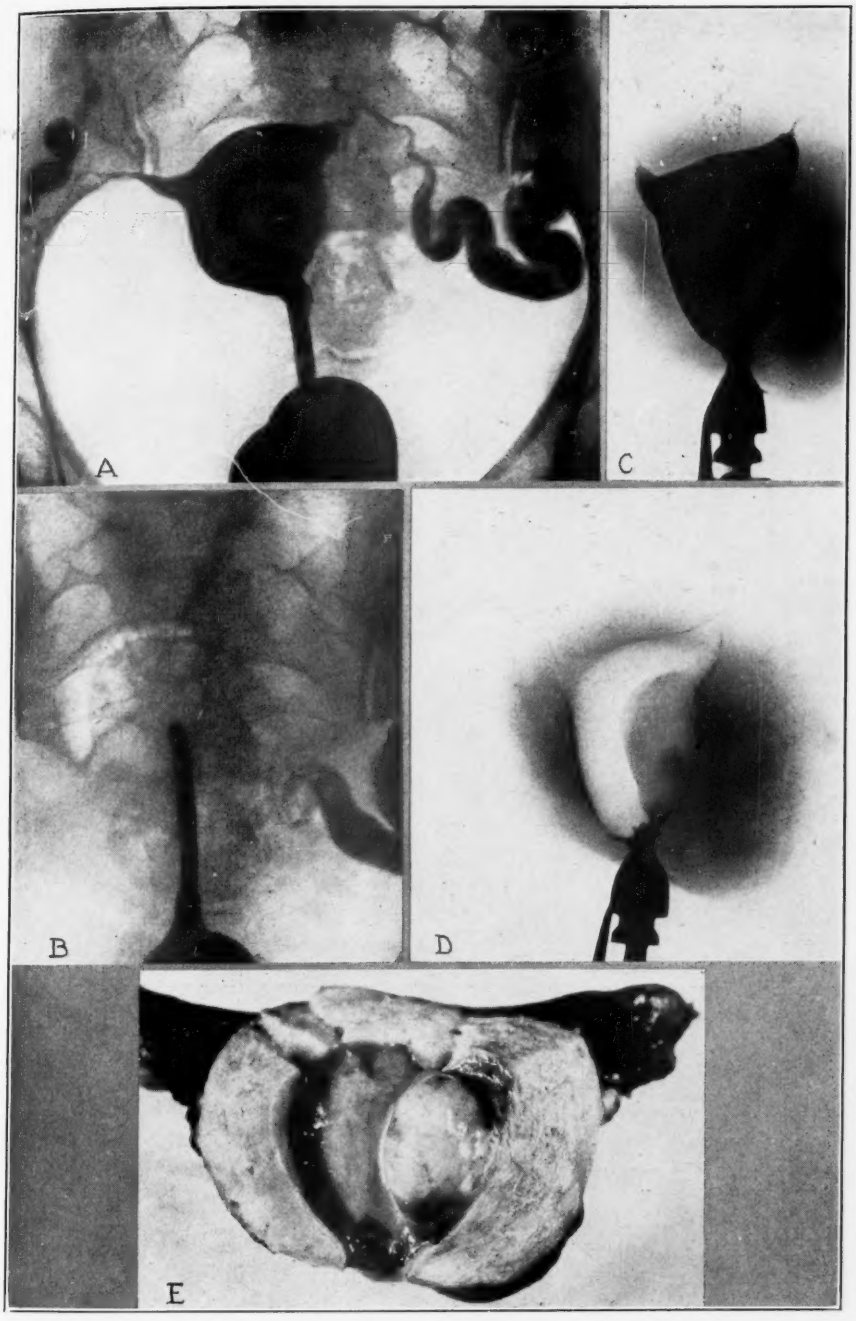
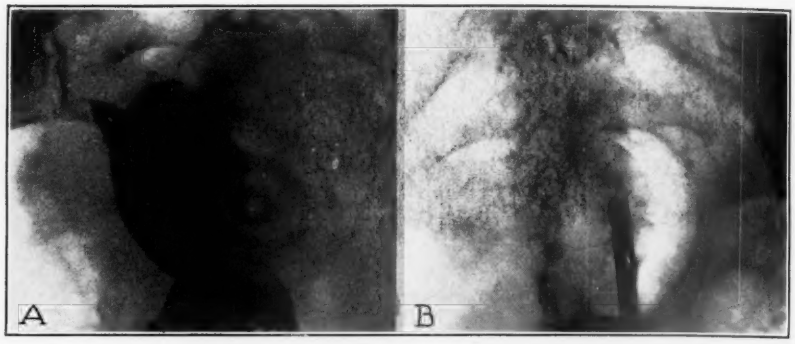
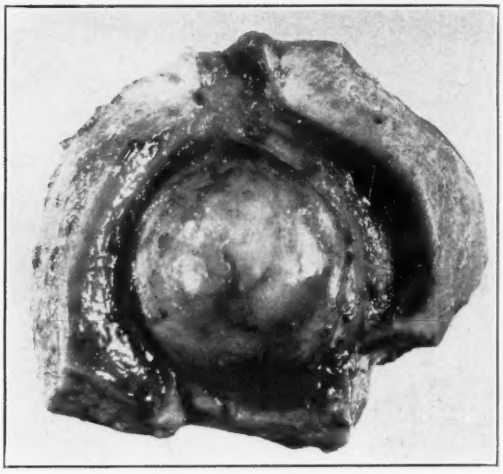


Fig. 3.—Case M. M. *A*, Clinical hyterogram with hippuran 100 per cent solution shows a dilated cavity without any definite indication of a submucous fibroid. *B*, Clinical hysteroaerogram with CO_2 injected after hippuran shows the uterine cavity to be definitely encroached upon by a submucous myoma. *C*, Hysterogram of extirpated uterus with hippuran 100 per cent solution; no indication of a submucous fibroid. *D*, Hysteroaerogram of extirpated uterus with CO_2 after hippuran shows the solitary submucous fibroid practically as it appears in Fig. 3, *E*. *E*, Uterus cut open shows the submucous fibroid visualized in hysteroaerogram, Fig. 3, *D*.





C.

Fig. 4.—Case I. G. *A*, Clinical hysterogram with hippuran 100 per cent solution shows an irregular shadow not particularly diagnostic of a submucous fibroid. *B*, Clinical hysteroaerogram with CO_2 injected after hippuran shows the submucous fibroid projecting into the uterine cavity as seen in the specimen (Fig. 4, *C*). *C*, Uterus cut open showing the solitary submucous fibroid.

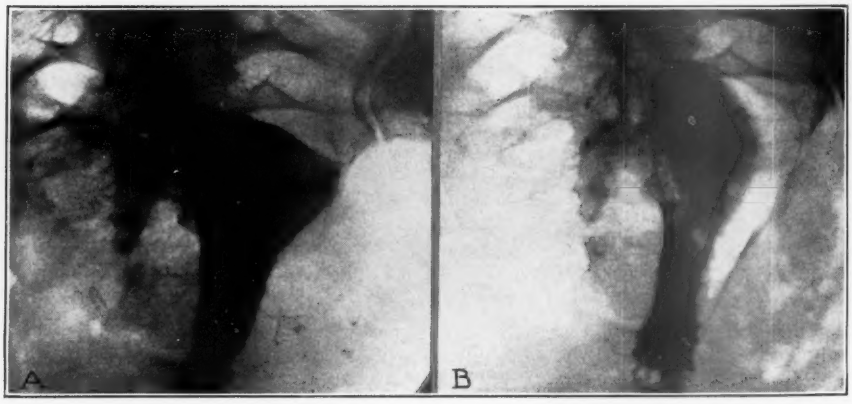


Fig. 5.—Case S. K. *A*, Clinical hysterogram with hippuran 100 per cent solution shows a dilated triangular uterine cavity; no suggestion of a submucous fibroid. *B*, Clinical hysteroaerogram with CO_2 injection after hippuran shows the submucous fibroid.

When no submucous myoma is present despite the multiplicity of the tumors, the uterine cavity may be typically triangular as in Fig. 8, *A* and *B*, Case M. E., where the cavity is only moderately dilated; or Fig. 9, *A* and *B*, Case T. B., where the cavity is very markedly dilated without any protrusion into it of any of the fibroids. The CO_2 x-ray contrast film, however, demonstrates this characteristically as may be seen in Figs. 9, *B* and 10, *B*. Solutions in the strengths employed for intravenous or retrograde urography are not quite strong enough to leave a deposit

Fig. 6.—Case P. B. *A*, Clinical hysterogram with hippuran 100 per cent solution shows a dilated crescentic uterine cavity suggestive of submucous myoma. The tubes have been entered by the hippuran. *B*, Clinical hysteroaerogram with CO_2 injection after hippuran shows the submucous nature of the tumor. The tubes are still seen to be filled. *C, After myomectomy.* Clinical hysterogram using hippuran 100 per cent solution showing a triangular uterine cavity. *D, After myomectomy.* Clinical hysteroaerogram after CO_2 injection shows a triangular uterine cavity; no protrusion into it.

upon the uterine mucosa to serve as contrast with CO_2. We found that strengths of 80 per cent and upward gave better results. CO_2 is preferable to air because it avoids all possibility of embolism, being absorbed by an equal quantity of blood, while air and its other components, oxygen and nitrogen, are relatively insoluble.

The indications for the use of x-ray and radio-opaque media and CO_2 for the demonstration of submucous myoma may be briefly given:

1. When it is important to avoid a laparotomy for fibroids as in the case of obese individuals and in systemic disease, in which circumstances x-ray and radium therapy are usually preferred. If a submucous myoma is positively known to be present, surgical removal is indicated despite the increased risk to the otherwise handicapped patient.

2. When considering myomectomy in younger individuals who are sterile and desire children, or when menstruation is to be conserved,

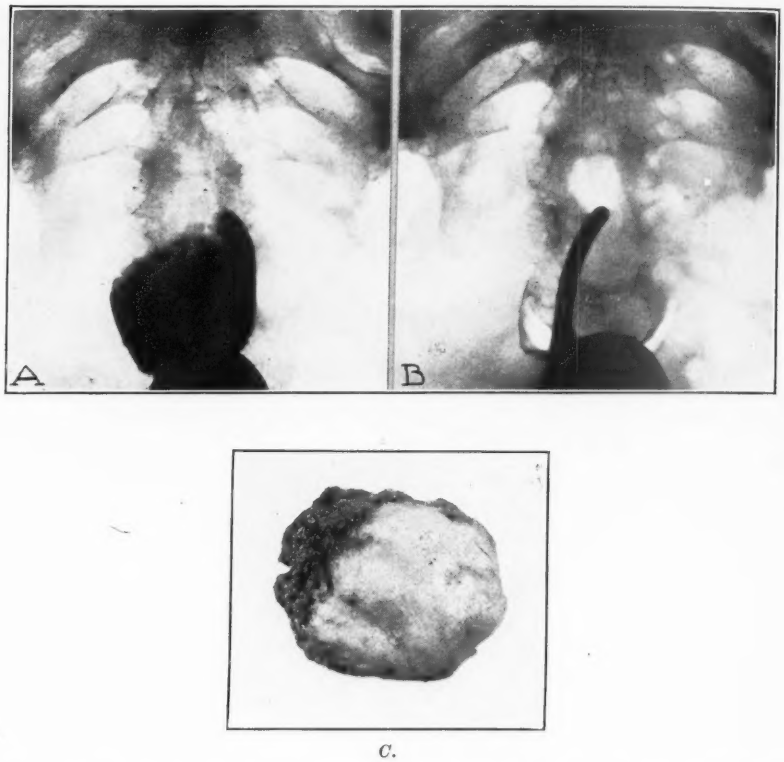


Fig. 7.—Case C. S. *A*, Clinical hysterogram with hippuran 100 per cent solution showing an irregular cavity without characteristic signs. *B*, Clinical hysteroaerogram with CO_2 injected after hippuran showing the submucous character of the tumor. *C*, Extirpated uterus cut open showing the submucous myoma.

the knowledge of the presence of a submucous myoma will enable the surgeon to deal adequately with the condition, adopting suitable vaginal or laparotomy technique, or a combination of the two.

The cases in which hippuran and CO_2 were employed are the following:

Case E. C., 52 years old, gravida ii, para ii; menorrhagia for two years, flow increasing from three- to an eight-day flow with clots. Uterus enlarged to the size of a four months' gestation. Hysterectomy and bilateral salpingo-oophorectomy. Specimen injected with hippuran and CO_2 showed multiple submucous fibroids (Figs. 1, *A* and 1, *B*).

Case B. H., 42 years old, gravida ii, para ii; complained of menorrhagia of one year's duration and severe dysmenorrhea, periods lasting six to seven days instead of three to four. Uterus enlarged to size of a two and one-half months' gestation; cervix normal; adnexa not palpable. Hysterectomy. Specimen revealed by hippuran and CO_2 a single plum-sized submucous fibroid on a sessile pedicle (Fig. 2, *C*).

Case M. M., 47 years old, gravida iii, para iii; menorrhagia and dysmenorrhea for the past four to five months, periods increased from four to eight days, the flow being

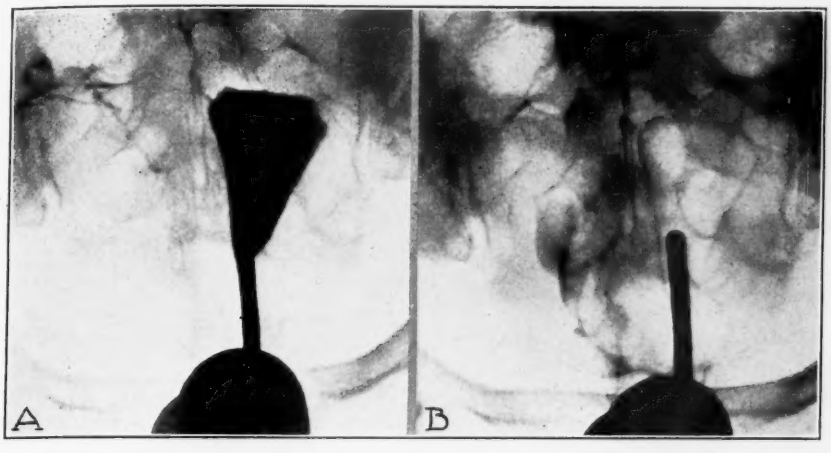


Fig. 8.—Case M. E. *A*, Clinical hysterogram with hippuran 100 per cent solution showing a somewhat dilated cavity with no suggestion of submucous myoma. *B*, Clinical hysteroaerogram after CO_2 injection shows a triangular cavity with no encroachment.

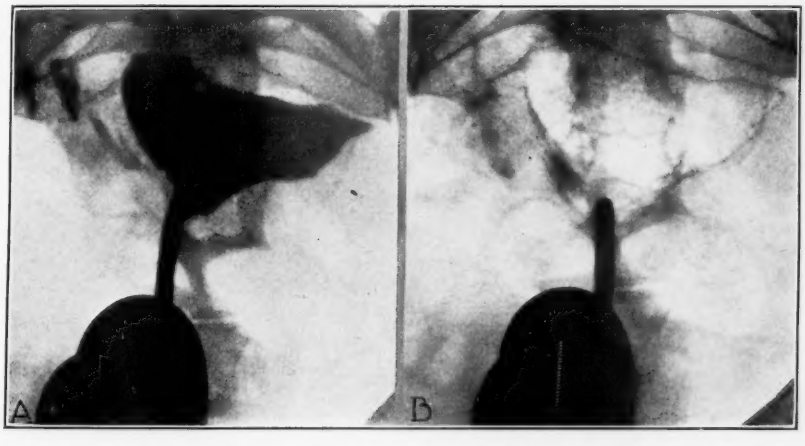


Fig. 9.—Case T. B. *A*, Clinical hysterogram with hippuran 100 per cent solution showing a widely dilated irregular uterine cavity. *B*, Clinical hysteroaerogram with CO_2 injected after hippuran showing no encroachment upon the uterine cavity.

profuse. Uterus enlarged to the size of a ten to eleven weeks' gestation; adnexa not palpable; cervix normal. Clinical hysterogram, hippuran and CO_2, showed a submucous myoma. Hysterectomy and bilateral salpingo-oophorectomy. Specimen showed a uterus enlarged to a three months' pregnancy, containing one large submucous fibroid and a few intramural fibroids (Fig. 3, *D*).

Case I. G., 43 years old, gravida ii, para ii; for past six months severe menstrual bleeding with passage of clots. Uterus uniformly enlarged to the size of a three

months' gestation. Clinical hysterogram, hippuran and CO_2, showed the presence of a large submucous myoma, Fig. 4, *B* (specimen), which was confirmed by the opened specimen.

Fig. 10.—Case F. W. *A*, Flat plate showing faint outline of enlarged uterus in relation to pelvis. *B*, Clinical hysterogram with hippuran 100 per cent solution showing a widely dilated irregular uterine cavity without any definite sign of submucous encroachment. *C*, Clinical hysteroaerogram with CO_2 injected after hippuran showing the submucous character of the fibroid. *D*, *After myomectomy.* Clinical hysterogram with hippuran 100 per cent solution showing widely dilated uterine cavity of triangular shape. *E*, *After myomectomy.* Clinical hysteroaerogram with CO_2 injected after hippuran showing a widely dilated uterine cavity; no submucous encroachment.

Case S. K., 48 years old, gravida v, para iv; craniotomy; and an angioma of the skull removed six months ago. Became pregnant, last period occurring on Dec. 20, 1937; an x-ray abortion was performed. Entered hospital bleeding profusely. Uterus the size of a three and one-half months' gestation and contained a number of subserous fibroids; cervix patulous; adnexa not palpable. Bleeding continued despite oxytocics, and a dilatation and curettage were performed. This revealed a submucous fibroid on the right posterolateral wall of the uterus, confirmed by a clinical hysterogram, hippuran and CO_2, Fig. 5, *B*.

Case P. B., 25 years old, single, gravida 0, para 0; menorrhagia for the past eight to nine months, flow increased from five to six to twelve to thirteen days. Uterus the size of a three months' gestation, smooth in contour, mobile; cervix firm, closed; adnexa negative. Clinical hysterogram (hippuran and CO_2) showed the presence of a submucous myoma (Fig. 6, *B*). Myomectomy was performed; one large fibroid removed from the left uterine wall. The postoperative injection of hippuran and CO_2 showed a return to the triangular form of the uterine cavity (Fig. 6, *D*).

Case C. S., 43 years old, married 9 years, gravida 0, para 0; menses normal until one year ago; since then has had menorrhagia and dysmenorrhea; flow eight to ten days with many clots. Uterus enlarged to size of a seven to eight weeks' gestation and slightly irregular; cervix softened and external os slightly dilated; adnexa negative. The lower pole of the intrauterine tumor was just palpable to finger tip. Clinical hysterogram not necessary but done for purposes of demonstration and contrast (Fig. 8, *B*). Vaginal hysterotomy and removal of a submucous fibroid the size of a large plum (Fig. 7, *C*).

Case M. E., 44 years old, gravida vi, para v; menorrhagia of one year's duration. Uterus enlarged to the size of an eight weeks' gestation due to a number of small myomas in the right uterine wall. Curettage: uterine cavity symmetrical showing no submucous tumors. Clinical hysterogram, hippuran and CO_2, showed moderately dilated triangular uterine cavity, no submucous myoma.

Case T. B., 49 years old, gravida ii, para ii; menorrhagia for past year. Blood pressure 200/100. Pelvic examination: cervix hypertrophied; uterus enlarged to the size of a two to two and one-half months' gestation; adnexa not palpable. Clinical hysterogram, hippuran and CO_2, showed the uterine cavity dilated but not encroached upon by any tumor (Figs. 10, *A* and *B*). Curettage and radium, 1,500 mc. hours.

Case F. W., 29 years old, single, nulligravida; profuse regular periods; increasing size of abdomen and metrorrhagia of three weeks' duration on two occasions. Uterus found enlarged to the size of five months' gestation, firm and tender. Clinical hysterogram, hippuran and CO_2, showed a markedly dilated, irregular uterine cavity on one side suggestive of a submucous myoma (Fig. 10, *B*) which was definitely proved after the injection of CO_2 (Fig. 10, *C*). A single large fibroid was removed without entering the endometrial cavity although the fibroid encroached upon the entire left side of the cavity. A hysterogram with hippuran and CO_2 after the operation showed the endometrial cavity of triangular configuration (Fig. 10, *D*) and after CO_2 injection (Fig. 10, *E*).

SUMMARY

The presence of submucous myomas can be diagnosticated roentgenologically by the intrauterine injection of hippuran followed by CO_2. Neither by itself is adequate for this purpose. The hippuran is used in concentrations of 80 to 100 per cent which, when expelled from the uterine cavity, leaves a crystalline deposit on the uterine mucosa and the mucosa covering the submucous tumor. The injection of CO_2 serves as a transparent contrast to the densely opaque hippuran outline. Both media are innocuous, each being well tolerated by the organism. There are no irritation and no residue or foreign body reaction. In selected cases where recognition of submucous myoma is important from the viewpoint of the choice of therapy, this method appears to be serviceable.

BREECH PRESENTATIONS AND PROPHYLACTIC EXTERNAL CEPHALIC VERSION

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MUCH has been written on the subject of breech presentation, its high fetal mortality and maternal morbidity, and the proper methods of delivering these patients. In many studies emphasis has been placed upon the management of the breech for the purpose of lowering the fetal mortality. Cannel and Dodek have shown in a review of the literature that, no matter what method is employed in delivering a breech presentation, the fetal mortality still remains too high. Further, it was shown that the greatest cause of fetal death is the result of injury rather than of asphyxia. It is our purpose to add to the literature the results of our study on breech presentations and to lay special emphasis upon the value of prophylactic external cephalic version as a prenatal method of treating breech presentations by which the fetal mortality may be materially reduced.

MATERIAL

We studied 167 primary breech presentations delivered at the University Hospital from 1926 to 1935. We eliminated all multiple pregnances where one or both babies were delivered as a breech, as well as all internal version and breech extractions.

In Table I are noted the distribution of the cases as to parity and types of presentations. It is interesting that the primigravida and multigravida are practically equal in number. This is somewhat unusual since breech presentations are usually considered more common in the multigravida.

In this same table we find that full breech and frank breech presentations, as well as the anterior types of breech presentations are in great preponderance.

In Table II are listed the various methods of delivery employed and the relationship of the fetal mortality to each type of delivery. Except for cesarean section deliveries we find that there is no marked difference in the fetal mortality and for each type the fetal mortality is high. In only two cases were the forceps applied to the aftercoming head.

It is interesting to know that in 39 cases of breech deliveries a single mediolateral episiotomy preceded the delivery; in 24 cases a bilateral episiotomy was used; and only in one case was a central episiotomy performed. Perineal lacerations were noted in 7 cases. This low incidence of lacerations is due to frequent use of episiotomy preceding most breech deliveries. In only one case was the Voorhees' bag employed to aid in the dilatation of the cervix, while in 8 cases manual dilatation of the cervix was necessary to effect delivery.

In attempting to find the etiologic factors responsible for the breech presentations exclusive of multiparity, we found that in 19 cases prematurity was present; in 2 cases monstrosity could be indicted; and in 58 cases contracted pelvis from a

TABLE I. SUMMARY OF BREECH DELIVERIES

Total number of primary breech deliveries		167
Primigravida	84	
Multigravida	83	
Full breech	52	
Frank breech	79	
Footling	14	
Not classified	25	
L. S. A.	72	
R. S. A.	74	
L. S. P.	10	
R. S. P.	6	
R. S. T.	1	
Not noted	4	

TABLE II. METHOD OF DELIVERY AND FETAL MORTALITY

TYPE OF DELIVERY	NO. OF CASES	MORTALITY
Breech extraction alone	71	27%
Break-up of breech and extraction	43	30%
Spontaneous delivery	38	41%
Cesarean section	12	0
Not noted	3	0

slight to a marked degree was noted. There were 12 cesarean operations done; in 8 cases for contracted pelvis; 2 for placenta previa; one for premature separation of the placenta; and one for the purpose of sterilization.

The duration of labor was found to be increased averaging 22.2 hours for the primigravida and 13.67 hours for the multigravida.

Very few accidents due to the breech presentation were encountered. Prolapse of the cord occurred in only 5 cases and in one case the arm was prolapsed as well. There were no clavicle nor femur fractures reported, and the only injury noted was a contusion of the thigh and arm in two cases.

TABLE III. CAUSES OF FETAL DEATH IN BREECH PRESENTATIONS

Intracranial hemorrhage		7
Asphyxia		21
Atelectasis		2
Monstrosity		2
Prematurity		7
Eclampsia		2
Maternal syphilis		4
Unknown		2
Total		47 (28.1%)

TABLE IV. FETAL DEATHS ASSOCIATED WITH OBSTETRIC ACCIDENTS

Total fetal mortality		47
Premature separation of the placenta	7	
Nephritic toxemia	1	
Eclampsia	2	
Hydramnios	1	
Syphilis	4	
Bandl's contraction ring	1	
Placenta previa centralis	1	
Pyelitis	1	
Monstrosity	2	
Prematurity	7	
	27	
Corrected fetal death	20 (12.1%)	

The gross fetal mortality in this series was 47 (28.1 per cent) with a corrected mortality of 20 (12.1 per cent). In Table III are listed the various causes of fetal death. In view of the fact that very few of these babies came to necropsy, it is most probable that the high number of fetal deaths ascribed to asphyxia was perhaps due to birth injury. In Table IV are listed the fetal deaths as they were associated with obstetric accidents.

There were three maternal deaths. One was due to multiple emboli following the delivery. Another was due to chronic myelogenous leucemia; and the third was due to shock and postpartum hemorrhage following premature separation of the placenta. It is felt that none of these deaths could be attributed to the type of presentation nor to the delivery.

The maternal morbidity was definitely increased; in 31 cases there was an elevation of temperature to 100.4° F. or more on two consecutive days. Most of these infections were mild. This gave us a morbidity of 18.56 per cent which is an expected finding in breech deliveries.

PROPHYLACTIC EXTERNAL CEPHALIC VERSION

From this study, which is essentially in agreement with all other studies on breech presentations and deliveries, we can readily understand the undesirability of the breech presentations and the inability to markedly improve our results by breech deliveries.

We must, therefore, look to some other method of handling the breech presentations that will make it possible to obtain more desirable results. External cephalic version seems to offer the one method by which this may be accomplished. If it is successful, we immediately convert a fetal mortality of approximately 15 per cent in breech presentations to one of 3 per cent in cephalic presentations.

King and Gladden; Irving and Goethals; and Cannel and Dodek recommend external cephalic version. Also the reports of Gibberd, Ryder, Bartholomew, McGuinness, Glassman, Végh, Thornhill and others who have performed external versions are convincing. Despite these favorable reports we still find either a resistance or an indifference among the profession to perform external version. Obstetric textbooks recommend that external versions should be attempted, yet we fail to teach this art to our students, and we hesitate to practice it upon our patients.

We have performed external version from the twenty-eighth to the thirty-eighth week of pregnancy; however, the best time is generally from the thirty-second to thirty-sixth week, although it should be attempted even at term or early in labor. The technic of external cephalic version we have employed is the same as described in any standard textbook on obstetrics. We believe it is important, however, to emphasize certain points in the procedure and to take certain precautions in performing a version. If the abdomen is well powdered, it will facilitate the movements of the hands over the abdomen. The version should be done slowly and gradually; if the uterus undergoes contraction, the baby is held in place but no further pressure is made until the uterus is relaxed. In this manner the turning is continued so that it may take ten or fifteen minutes before the version is completed. The fetal heart beat should be obtained before, during, and for several minutes after the version in order to ascertain its rate, regularity, and character. In this manner we make certain that there

is no marked change in the fetal heart due to the version. We have often noted a temporary change in the rate and regularity of the fetal heart following a version but never a persistent one. If the fetal heart after five minutes of auscultation should show a persistent slowing or increase or irregularity, it would probably be safer to undo the version. We do not advocate the use of an anesthetic, because it carries with it the risk of employing too great a force which may result in premature separation of the placenta. We feel that if a version cannot be performed without an anesthetic, it is better to leave it undone, because it is probably due to two causes; (1) the breech is already tightly fixed in the pelvis; or (2) a frank breech may be present. If a version cannot be done with a reasonable amount of pressure then an x-ray picture should be taken to ascertain the type of presentation. If a frank breech is present, a version should not be done: (1) the extended legs splint the body so that the baby cannot be made to flex sufficiently to make the version easy; (2) a compound presentation may result.

McCullogh reports 4 cases of external version in unrecognized frank breech presentation. These patients were permitted to go into labor and allowed to remain in labor for many hours without recognizing that the dystocia was due to a compound presentation; both feet and head presenting at the same time, with the final outcome being rupture of the uterus in all four cases. In our series we found two cases where the external version was unsuccessful; the x-ray picture showed frank breech presentations.

Since 1936 we have attempted to perform external cephalic version upon breech presentations which have come under our observation. These cases were gathered from the University Obstetrical Clinic, the Baltimore City Hospital and Baltimore City Health Department Pre-Natal Clinics, the Franklin Square Hospital and from the senior author's private case files. We have followed 77 cases of breech presentations; in 68 cases versions were attempted and in 55 versions were successful and delivered as cephalic presentations. In 2 cases versions were successful, but later the presentations reverted to breech and delivered as such. In 9 cases versions could not be performed. In 3 cases version was unsuccessful but spontaneous versions occurred later. In 6 cases no version was attempted and spontaneous version took place. In 3 cases of transverse presentation in which the breech was the original presentation version was successful.

TABLE V. TOTAL NUMBER OF BREECH PRESENTATIONS FOLLOWED (77)

No. of versions attempted	68
No. of successes	55 (81%)
No. of primigravida	21
No. of successes in primigravida	15 (71.4%)
No. of multigravida	47
No. of successes in multigravida	40 (85.3%)
Resulting Presentations:	
Occiput anterior	43 (78.2%)
Occiput posterior	7
Rotation from occiput posterior or occiput transverse to occiput anterior	5
Gross fetal mortality	1 (1.82%)

In Table V we give a summary of our results on external versions. It is important to point out the 71.4 and 85.3 per cent successes in primigravida and multigravida, respectively, as well as the 78.2 per cent resulting anterior occiput presentations,

In 14 cases the pelvis was contracted. A total of 22 forceps deliveries were performed; 13 of these were forceps deliveries done for convenience and 9 for indicated reasons. There were 4 cesarean operations; 3 in vertex presentations for disproportion and one in a breech presentation where version failed and a contracted pelvis was present.

TABLE VI. COLLECTED CASES OF EXTERNAL VERSION

AUTHOR	CASES ATTEMPTED	CASES SUCCESSFUL	NO. WITH ANESTHESIA	PRIMIPARAS	MULTIPARAS	FETAL MORTALITY	PROLAPSE CORD	BLEEDING PREMATURE SEPARATION OF PLACENTA	COMPOUND PRESENTATION	REMARKS
Vedder	52	46	22			1 (2.18%)	0			
Thornhill	58	49	2	17	32	1 (2%)	0			2 sections
Mehta	55	53	0	8	47	0	0			
Davison	14	12	0			0	0			
Donovan	91	80	-	38	42	4 (5%)	0			
McGuinness	59	57	2	23	34	1 (1.8%)	0			
Glassman	64	61	0	9	52	0	0			
Ryder	29	20	6			0	0	1 (slight)		
Gibberd	232	179	5			7 (3.9%)	0	1 (slight)		
Rietdijk	356	317				12 (4.5%)	2			
Meurer	149	138								Quoted by Bartholomew
Kouwer	190	174	0			7 (4%)				
Meyer	22	21	0	3	18	1 (4.5%)			1	
Decugniere	32	29	0	12	17	0				1 Cesarean delivery
Saroey	23	20								Quoted by Horn
Pollack	16	16	7							
Bartholomew	54	39		53%	80%	0	0	0	0	
Aranowitch	66	36								Quoted by Horn
Végh	36	32	0	16	20	0		0		
Kende	7	6				0				
King, W. W.		250	38			4%				
White		300	92			5%		6		All 6 cases of bleeding under anesthetic
Allen		100		35	65	0				
Macaffee		134				0.74%				
Wrigley	76	45	76			10 (13.6%)	1	3		All cases done under an anesthetic
Siegel and McNally	68	55	1	15	40	1 (1.82%)	1	0	0	4 sections
Total		2269				3.13%				

Accidents due to the versions were practically none. There was no bleeding. There were only 2 cases of premature rupture of the membranes; 1 occurred twenty-four hours after and the other several days after the version. There were no premature labors. There was one case of prolapse of the cord and hand. This was in a multipara where version was performed early in labor and was successful. The labor progressed normally; the cervix became fully dilated and while the patient was being prepared for delivery her membranes ruptured with such great force that the amniotic fluid struck a wall about eight feet away. With this accident the cord and hand prolapsed together; the patient was immediately delivered of a live baby.

There were no maternal deaths and a maternal morbidity of 13 per cent resulted; all infections being mild.

There was one fetal death in the entire series of successful versions. This baby was delivered spontaneously at home before the arrival of the doctor, who found the baby lying in a pool of amniotic fluid with a loop of cord about its neck. This baby evidently died of external asphyxia from drowning.

In our series of 58 patients only one version was necessary; in 5 patients, 2 versions; in 2 patients, 3 versions; and in 1 patient, 4 versions were done. There apparently is no danger in performing repeated versions. At no time did we employ abdominal binders nor do we believe them to be of value.

Bartholomew reports that by performing external versions he had reduced the incidence of breech deliveries by 80 per cent. The incidence of breech presentations at the University Hospital for ten years prior to 1936 was 5.43 per cent. For the years 1936 and 1937, by performing a limited number of external versions since not all breech presentations came under our care, this incidence was reduced to 3.78 per cent.

DISCUSSION

The objections to performing external cephalic version are generally given as premature rupture of the membranes; premature labor; premature separation of the placenta; prolapse of the cord; twisting of the cord about the baby's neck or body; reversion back to breech; compound presentation; rupture of the uterus; intrauterine death and finally that spontaneous version does occur. These are all valid objections but to determine their frequency and their effect upon the fetal mortality, we have gathered together in Table VI the reports of many writers on this subject. From this we find that the gross fetal mortality except for Wrigley's series varied from 5 per cent to nothing. In Wrigley's series we find that all the versions were done under anesthesia with a high incidence of bleeding and resultant high fetal mortality. Wrigley warns against the use of anesthesia, because of the too great force employed in executing the version. Otherwise the complications following versions were very few. Thus in a total of 2,269 successful versions, there resulted a gross fetal mortality of 3.13 per cent, which is what one expects even in cephalic presentations.

We recommend doing a cephalic version in the face of existing contracted pelvis as a valuable procedure. It is impossible to adequately judge disproportion clinically in the case of a breech presentation; and roentgen cephalometry is very unsatisfactory in these cases. Goethals has shown that the technic is complicated and that in 39 per cent of the films taken, measurements could not accurately be made. In cephalic presentations the x-ray measurements are more

satisfactory and clinically one can determine whether disproportion exists and whether a test of labor should be given. We wish to report four cases which graphically illustrate the value of cephalic version in contracted pelves:

CASE 1.—A 16-year-old negress, primigravida with a rachitic pelvis whose C.D. measured 9.0 cm. and x-ray C. V. 8.4 cm. was seen on July 13, 1937 with a presentation of L. S. T. and converted by external version to L. O. A. A test of labor was given, the head entered the pelvis and after a labor of 12¼ hours delivered spontaneously of a live baby weighing 6 pounds and 1 ounce. With these measurements and failure to have performed a version, we would have delivered her by an elective cesarean operation.

CASE 2.—A 19-year-old white woman, para i who, in her first pregnancy, had a breech presentation with the breech fixed in the pelvis. Attempts were made to perform an external version with and without an anesthetic but failed. X-ray cephalopelvimetry showed a borderline disproportion with a frank breech. She was delivered by an elective section of a live baby weighing 6 pounds 7 ounces. In her next pregnancy on Sept. 17, 1936 she was thirty-four weeks with an L. S. A. An external version was done changing the presentation to R. O. A. At term a test of labor was permitted, the head entered the pelvis and after a labor of twelve hours and ten minutes, she was delivered by low forceps after a manual rotation from R. O. T. to R. O. A. of a live baby weighing 6.5 pounds. Had we failed to have done the version in this case she would have been delivered by a second cesarean section.

CASE 3.—A 21-year-old negress, gravida iii, who had a generally contracted pelvis, was delivered in her first pregnancy of a stillborn baby by cesarean section. The reason for the section was not known. In her second pregnancy she had a breech presentation with no attempt at conversion. It resulted in a footling presentation and during the extraction both arms became extended in the nuchal position, the clavicle was accidentally fractured and finally a live baby weighing 6 pounds 2½ ounces was delivered. With her third pregnancy on Oct. 6, 1936 an L. S. P. was converted by external version to R. O. T. She was delivered on Dec. 2, 1936 after a labor of eight hours and fifty-four minutes by low forceps after manual rotation from R. O. P. to R. O. A. of a live baby weighing 6 pounds 4½ ounces. Thus in this case we obviated the difficulties of a breech delivery.

CASE 4.—A 21-year-old negress, primigravida, with a contracted pelvis had on Sept. 29, 1937 an L. S. A. at thirty-eight weeks converted by external version to R. O. T. On Oct. 13, 1937 she went into labor with suggestive disproportion and was given a test of labor. The head failed to enter the pelvis and she was delivered by a low cervical section of a live baby. If this case had been permitted to have remained a breech, a test of labor would have been of no real value, because the soft breech would enter the pelvis, whereas, the aftercoming head would not; and it would have been too late then to perform a cesarean section.

There have been reported sporadic cases of fetal death in utero following external version. That has not been our experience nor that of most writers. It is quite possible that these deaths may have been coincidental, since a certain number of babies die in utero without any discernible cause.

SUMMARY

1. A study of 167 primary breech deliveries is presented.

2. The etiologic factors responsible for breech presentations aside from multiparity seem to be prematurity, monstrosity, and contracted pelves.

3. This study reveals a gross fetal mortality of 28.1 per cent and a corrected one of 12.1 per cent.

4. It is believed that the fetal mortality in breech deliveries cannot be reduced below a certain minimum, which is still too high, due to inherent anatomic difficulties present.

5. External cephalic version offers a satisfactory method by which the high fetal mortality in breech deliveries can be reduced.

6. In this series external version was successful in 81 per cent of the cases with the resultant presentation being occiput anterior in 78.2 per cent.

7. External version should be performed without anesthesia, slowly with auscultation of the fetal heart before, during, and after the version.

8. If version cannot be performed with a reasonable amount of force, an x-ray picture should be taken to rule out a frank breech, which should not be turned.

9. Carefully done external versions result in few accidents and in good outcome for the baby.

10. An external version in the face of a contracted pelvis is desirable in order that better clinical judgment may be used in the treatment of the case.

11. The practice of external cephalic version as a prophylactic measure in prenatal care should be taught and employed in order to reduce the incidence of breech deliveries with its high fetal mortality.

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During 1914 to 1933 there were 47,793 deliveries at the Helsingfors Woman's Clinic. During the first ten-year period there were 22,196 deliveries with a maternal death rate of 0.45 per cent. During the remaining years there were 25,597 deliveries with a mortality of 0.30 per cent. The most important causes of death were infection (61.8 and 45.9, respectively) toxemia (23.7 and 27.1 per cent), hemorrhage (9 and 8 per cent), and heart trouble (5 and 12 per cent). About 50 per cent of the patients who died were infected or moribund at the time of admission to the hospital. If these are excluded, the total maternal mortality for the two periods was 0.18 and 0.17 per cent, respectively.

J. P. Greenhill.

THE EFFECT OF QUININE-CALCIUM ON UTERINE MOTILITY

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ALTHOUGH quinine has long been recognized as an ecbolic drug, the results obtained with its therapeutic use have been variable and unpredictable.

Schübel[1] working on puerperal cats found that small doses of quinine amplified the uterine contractions while large doses depressed them, and he emphasizes therefore the importance of using small doses in obstetric practice. Weissmann and Klippel[2] on the other hand have not seen any depressing effect with larger doses of quinine, and they attribute the variable effects to differences in uterine sensitivity. In studying the effects obtained with combinations of quinine and various other oxytocic agents, Kunisho[3] found no potentiation of pituitrin effects with quinine on strips of human uterus, whereas in the case of excised rabbit uteri, pregnant or nonpregnant, he[4] found a combination of one-half the minimal active dose of each drug to be an effective stimulus.

More recent investigations have indicated that quinine is much more effective in increasing uterine motility when it is combined with calcium.

Winkler and Vetter[5] and Weissmann and Klippel[2] in clinical studies have reported very good results with quinine-calcium (Sandoz). They found that it greatly surpassed quinine alone not only in increasing the sensitivity of the uterus to pituitary extract but also for inducing labor pains. The main indication according to their investigations is primary uterine inertia particularly after premature rupture of the fetal membranes.

Weissmann and Klippel extended their work into the experimental field and tested quinine and calcium separately and in combination on multiparas and nonpregnant mice. The animals were killed shortly after application of the respective drugs, and kymographic registrations were made of the contractions of the surviving uteri. The contractions after quinine alone showed an increase in both frequency and amplitude, while with calcium alone only the amplitude was increased. When quinine and calcium were administered simultaneously the records showed a combination of the quinine and calcium curves.

Other investigations[6, 7] have indicated the usefulness of quinine-calcium in therapeutic abortions, and Busch[8] has employed it in the treatment of a variety of obstetric cases.

In the present investigation the uterine fistula for recording uterine motility in unanesthetized rabbits[9, 10] was used. Fully mature female rabbits, weighing from 2 to 3 kilograms, were ovariectomized and motility was induced and maintained by daily administration of the ovarian hormone, estradiol.

The preparations used were a solution of quinine dihydrochloride, the neocalglucon (calcium gluconogalactogluconate) ampoule product equivalent in calcium ion content to a 10 per cent supersaturated solution of calcium gluconate, and the regular quinine-calcium (Sandoz).[1] Each cubic centimeter of the quinine-calcium (Sandoz) ampoule product is said to contain 0.06 gm. of quinine gluconate

(equivalent to 0.037 gm. of anhydrous quinine base) and 0.009 gm. of calcium ion. These quantities of quinine (calculated as the anhydrous base) and calcium ion were contained respectively in each cubic centimeter of the quinine dihydrochloride solution and the neo-calglucon ampoule solution. Injections were made both intravenously and intramuscularly, in the former case the usual dose being 1.0 c.c. and in the latter 2.0 c.c. The rate of intravenous injections never exceeded 1.0 c.c. per minute.

The plan of procedure which was adopted for the most part was to run comparable experiments, so far as conditions permitted, using the various preparations on consecutive days on the same animal. This was deemed advisable for two reasons: (1) The effect from the quinine injections, even after intravenous administration, was found to last for as long as 1.5 to 2 hours; (2) in control experiments where no injections were made, uterine motility sometimes decreased appreciably within two

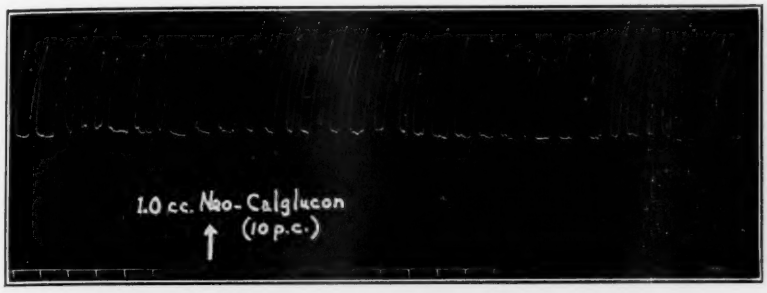

Fig. 1.—Effect of neo-calglucon (1.0 c.c. intravenously) on uterine motility. Time in minutes.

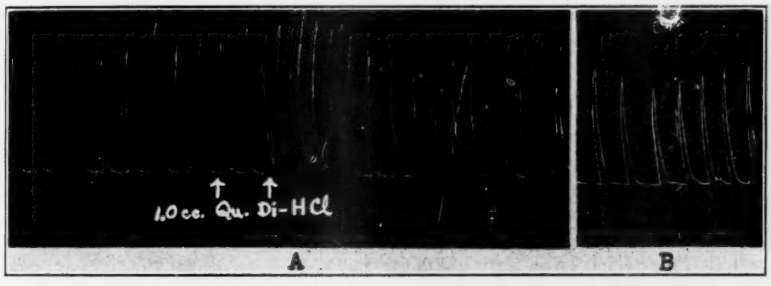

Fig. 2.—Effect of quinine dihydrochloride (1.0 c.c. intravenously) on uterine motility. (*A*) Immediately after, (*B*) one hour after injection. Time in minutes.

to three hours so that repeated injections might give unreliable and incomparable results.

The procedure was varied somewhat in different experiments but the general rule was to allow fifteen to thirty minutes of normal recording and then make the injection without interrupting the record. In order to evaluate the records the height of each separate contraction was measured, and for comparing any given period with the normal the total contraction height for this period was divided by the number of minutes. Since it was necessary to establish a new normal for each separate experiment, the only way of comparing the effects of different injections was to express the results as percentage variation from the normal.

EXPERIMENTAL RESULTS

The records in general show that while quinine and calcium both produce an increase in uterine motility the effect produced by a combina-

tion of the two is appreciably greater and more prolonged than that with either alone. This is true for both intravenous and intramuscular injections.

Figs. 1 to 3 are typical records showing the effects of intravenous injections. In all three the increased motility is due primarily to an increase in the height of contractions, the rate showing no appreciable change except during the first few minutes after the injection when it is usually accelerated. In the case of both quinine preparations (Figs. 2 and 3) there is always a tendency for a sustained contraction for the first two or three minutes which becomes more pronounced if the injection is made with greater rapidity (see Fig. 4). This effect was not produced with calcium. The more prolonged effect of quinine-calcium as compared with that of quinine alone is shown by the records in part *B* of Figs. 2 and 3 which were made

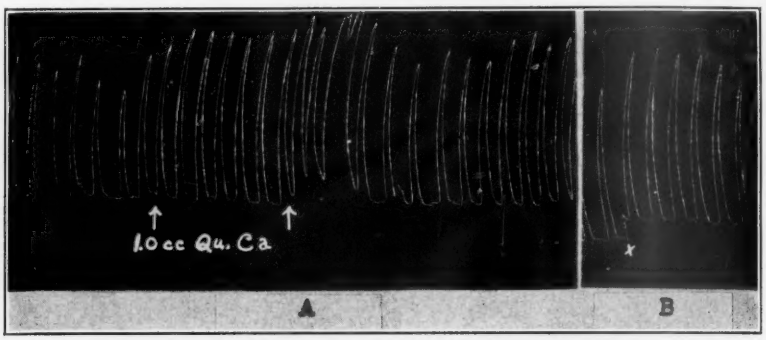

Fig. 3.—Effect of quinine-calcium (1.0 c.c. intravenously) on uterine motility. (*A*) Immediately after, (*B*) one hour after injection. Time in minutes. Base line readjusted at *X*.

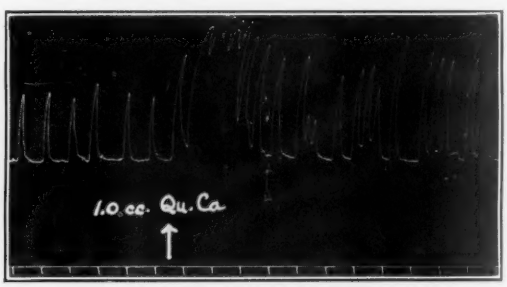

Fig. 4.—Effect of a more rapid injection of quinine-calcium (1.0 c.c. intravenously) on uterine motility. Time in minutes.

one hour after the injections. While the uterine motility in the quinine record has returned to normal, it is still markedly increased in the experiment where quinine-calcium was used.

A careful measurement of the records from a number of experiments shows that during the first thirty minutes after intravenous injections of 1.0 c.c. each of the three preparations used, the greatest increase in motility is given by quinine-calcium. The average figures obtained by such an analysis, expressing the increase in per cent, were: for quinine-calcium 33, for quinine alone 18.7, and for calcium alone 26.5.

When the injections are made intramuscularly the results are essentially the same except that the effects appear more gradually and continue longer. The tendency for sustained contractions with quinine is less evident and is often absent altogether. In Figs. 5, 6, and 7 are records showing the effects at periods up to two hours after intramuscular injections of neo-calglucon, quinine dihydrochloride and quinine-cal-

cium, respectively. There is a marked increase in uterine motility with each of the three preparations, but with a combination of quinine and calcium the effect is greater than with either alone. This difference becomes more pronounced in parts *B* and *C* which were recorded at forty-five and eighty-five minutes after the injections

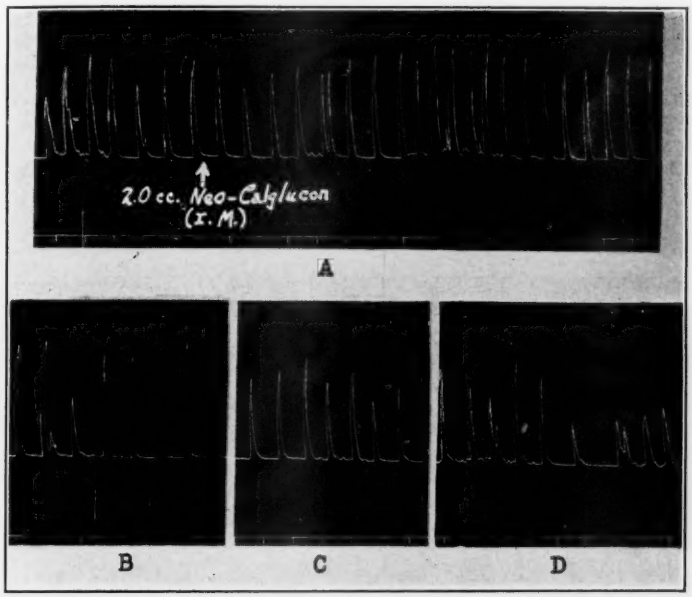

Fig. 5.—Effect of neo-calglucon (2.0 c.c. intramuscularly) on uterine motility. (*A*) Immediately after, (*B*) forty-five minutes after, (*C*) eighty-five minutes after, and (*D*) two hours after injection. Time in minutes.

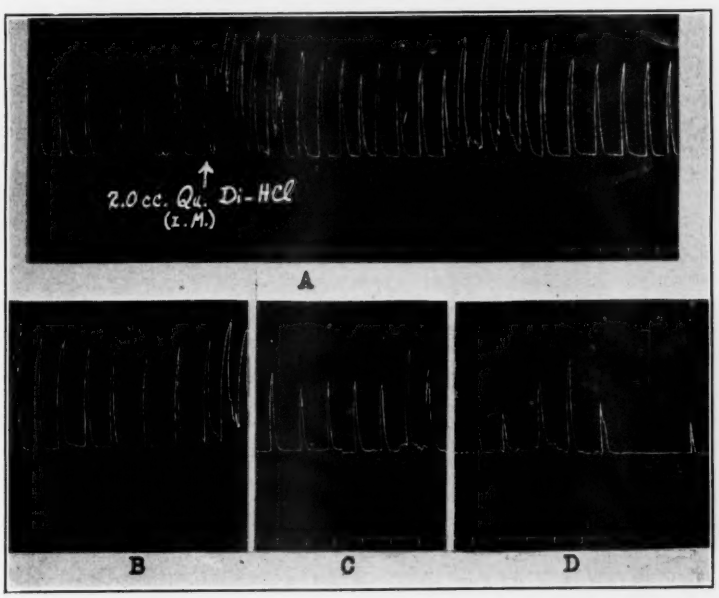

Fig. 6.—Effect of quinine dihydrochloride (2.0 c.c. intramuscularly) on uterine motility. (*A*) Immediately after, (*B*) forty-five minutes after, (*C*) eighty-five minutes after, and (*D*) two hours after injection. Time in minutes.

were made. In part *D* (two hours after injection) of the records where calcium and quinine were used alone, the motility is decreased noticeably below the normal. The significance of this decrease seems doubtful in view of the fact that motility may begin to decrease after two hours of continuous recording in control experiments where no injections have been made. It is significant, however, that the motility two hours and even longer (see Table I) after quinine-calcium is approximately normal, whereas it may be depressed as much as 50 per cent the same length of time after an equivalent dose of quinine alone.

Table I which has already been referred to summarizes the data taken from the entire experiments shown in Figs. 5 to 7. These three experiments were run on the same animal on three consecutive days under practically identical conditions. After ninety minutes of continuous recording following the injections the record was stopped for thirty minutes. Changes in motility were computed over ten-minute intervals throughout, and with very few exceptions the values for quinine and calcium combined are seen to be definitely larger than for either quinine or calcium alone.

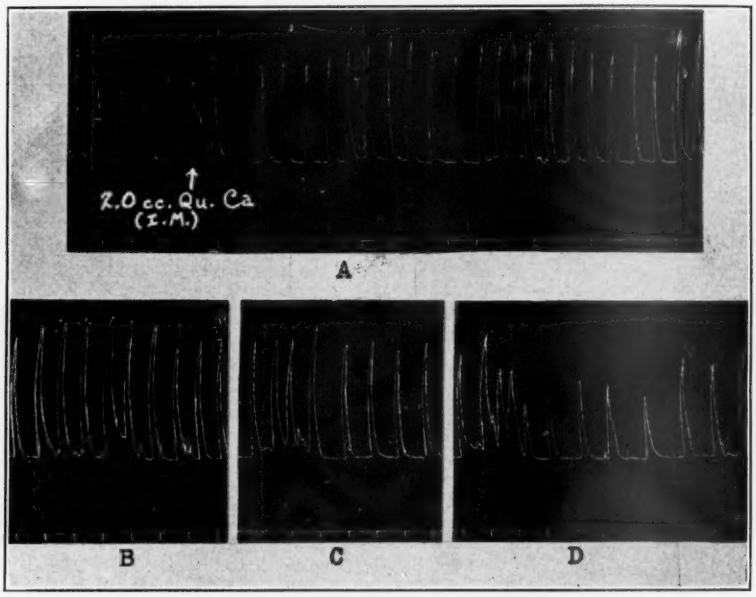

Fig. 7.—Effect of quinine-calcium (2.0 c.c. intramuscularly) on uterine motility. (*A*) Immediately after, (*B*) forty-five minutes after, (*C*) eighty-five minutes after, and (*D*) two hours after injection. Time in minutes.

As in the case of intravenous administration the calcium alone gives somewhat greater increases than the quinine alone. This of course may be purely a matter of dosage.

DISCUSSION

While the scope of this investigation is rather limited, particularly regarding the matter of dosage, the results are quite clear-cut. In the unanesthetized, nonpregnant rabbit with good uterine motility, quinine (in the dosage used) produces a greater effect when combined with calcium than when it is administered alone.

That calcium may have a stimulating effect upon uterine motility has been demonstrated both clinically and experimentally. Pieri[11] found that the weakened uterine contractions in a case of eclampsia were strengthened markedly after the injection of calcium. Reynolds[12] re-

TABLE I. CHANGES IN UTERINE MOTILITY FOLLOWING INTRAMUSCULAR INJECTIONS OF 2.0 C.C. EACH OF NEO-CALGLUCON, QUININE DIHYDROCHLORIDE AND QUININE-CALCIUM (SANDOZ). CHANGES ARE EXPRESSED AS PER CENT DEVIATION FROM THE NORMAL FOR TEN-MINUTE INTERVALS UP TO THREE HOURS

TIME AFTER INJECTION IN MINUTES	NEO-CALGLUCON (CALCIUM GLUCONOGALACTO-GLUCONATE)	QUININE DIHYDROCHLORIDE	QUININE-CALCIUM (SANDOZ)
0-10	+63	+91	+66
10-20	+64	+46	+97
20-30	+90	+56	+94
30-40	+79	+15	+79
40-50	+20	+44	+70
50-60	+47	+18	+60
60-70	+48	+33	+59
70-80	+39	+40	+30
80-90	+25	+29	+44
Record Stopped for 30 Minutes			
120-130	-22	-62	+ 5
130-140		-42	- 6
140-150		-51	- 7
150-160		-75	+ 8
160-170		-40	-21
170-180			+13

cording from uterine fistulas in unanesthetized rabbits obtained sustained contractions with intravenous and subcutaneous injections of calcium. That the effect is due to the calcium ions is supported by the fact that identical results are produced by calcium chloride and calcium gluconate and furthermore by the fact that the contractions can be inhibited by magnesium salts. In the present work the effect of the calcium has been primarily one of increased amplitude of contractions, with no indication of sustained contractions. Since the two investigations were carried out under almost identical conditions except for the time of year, the question arises as to whether the sensitivity of the rabbit's uterus may not undergo a seasonal variation.

The manner in which calcium potentiates the quinine effect on the uterus is not clear. The tracings obtained by Weissmann and Klippel[2] from the surviving mouse uterus after giving quinine and calcium together show a combination of two quite distinct effects which are produced by the quinine and calcium separately, viz., increased rate of contractions and increased amplitude of contractions. In the rabbit uterus, however, neither drug acting separately nor the combination of the two affects the rate appreciably, the amplitude only being increased. While the increase in motility after quinine-calcium is not equal quantitatively to the combined increases after equivalent amounts of quinine and calcium separately, the potentiation of effect may be simply of an additive nature. On the other hand this does not seem to explain adequately the more prolonged effect of quinine-calcium as compared with that of quinine or calcium alone.

Judging from the results that have been obtained with quinine therapy, there can be little doubt that the sensitivity of the uterus to quinine must vary greatly under different natural and experimental conditions. And while calcium alone may have the ability to augment

uterine motility, it is entirely possible that when given in combination with quinine it may also increase the sensitivity of the uterine muscle to the action of quinine.

Although no attempt has been made to compare the effect of quinine-calcium with that of quinine under conditions of poor uterine motility or in animals during pregnancy, the favorable clinical reports seem to indicate that under such conditions the combination of these two products may have equally great or even greater potentiating effects.

SUMMARY

In the unanesthetized, nonpregnant rabbit, exhibiting estrin motility of the uterus, quinine-calcium produces a greater increase in uterine contractions than equivalent amounts of quinine or calcium given alone. The increase is due primarily to an increase in the amplitude of contractions, the rate remaining practically unchanged. The effect lasts for 1.0 to 1.5 hours after slow intravenous injections and for two to three hours after intramuscular injections.

NOTE.—Neo-calglucon and quinine-calcium (Sandoz) were made available through the courtesy of the Sandoz Chemical Co.

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Married couples who become the parents of a congenitally malformed child and who contemplate having additional children, frequently inquire regarding the possibility that any subsequent offspring will also be defective. A consecutive series of 275 families, each known to have possessed a congenitally malformed or defective child and also one or more subsequent members, was interviewed with regard to the outcome of all conceptions of the mothers.

Thirty-four, or approximately 12.4 per cent, of the families gave rise to one or more additional congenitally malformed members.

Among 431 conceptions that followed the birth of the malformed child, 331, or 76.8 per cent, ended in the birth of full-term, normally developed offspring. The remaining 100, or approximately one in four of the subsequent conceptions, ended in 43 congenitally malformed children, 42 miscarriages, 9 premature births, and 6 stillbirths. In families having one congenitally malformed child, a second one was born once in every 8.9 births, whereas in the general population a congenitally malformed infant appeared only once in every 213 births.

From this study it is concluded that offspring with congenital malformations, serious enough to warrant being recorded on death certificates, is approximately twenty-four times as likely to occur in families possessing a congenitally malformed child than in the population at large.

GROVER LIESE.

ROUTINE ROENTGEN PELVIMETRY IN 600 PRIMIPAROUS WHITE WOMEN CONSECUTIVELY DELIVERED AT TERM*

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ROENTGEN methods of pelvimetry have been in use in this clinic for a considerable period and during the past four years we have employed these methods routinely in primiparous patients. Early in 1937 I[1] reported our findings in the first 300 white women in whom this routine was carried out and later in the same year[2] the results in 450 white women were published. It is our opinion that the value of roentgen pelvimetric methods may be demonstrated best by the study of a group of women consecutively delivered at term (child 2500 gm. or over) in whom the influences of race, multiparity, and premature birth are not present. Obviously, it is the primiparous woman who should derive the greatest benefit from the knowledge of the true size and conformation of the bony pelvis. Furthermore, the conduct of labor in such patients will always remain one of the chief concerns of the obstetrician.

The present studies are based on the findings in 600 white primiparous women consecutively delivered at term in the wards of New Haven Hospital in whom roentgenometry of the pelvis has formed part of the routine prenatal program.† I propose to discuss in particular some of the problems of labor in this group and to point out the aid that such roentgenometric methods have given us. I shall consider only briefly the variations of the pelvis which we classify according to the dimensions found at the superior strait as follows:

Dolichopellic type: The anteroposterior diameter is longer than the transverse. In appearance the pelvic inlet is elongated anteroposteriorly.

Mesatipellic type: The anteroposterior and transverse diameter are of equal length or the anteroposterior diameter is slightly shorter than the transverse (never more than 1 cm.). In appearance the pelvic inlet is round.

Brachypellic type: The anteroposterior diameter is 1 to 3 cm. shorter than the transverse. In appearance the pelvic inlet is elongated transversely.

Platypellic type: The anteroposterior diameter is 3 cm. or more shorter than the transverse. The pelvic inlet is definitely flattened in its anteroposterior aspect.

When pelvic characters generally known as android changes, including narrowed forepart, funnel outlet, narrowed notch, etc., are present, such changes are noted in association with the above. In addition, we subdivide each of the above groups into large, average, and small pelves. Those interested in this complete classification are referred to one of my articles.[3] It is our feeling that the use of the terms dolichopellic, mesatipellic, etc., is more correct and more useful as a basis for the classification of pelvic variations than terms which may suggest etiologic factors concerning which we know so little.

*This study was made possible through the Research Funds of Yale University School of Medicine.

†In a few instances patients to whom no prenatal care has been given by us have entered our wards far advanced in labor. In such cases roentgenometry was carried out before the patient left the hospital. The number of those cases represents less than 1 per cent of the entire series.

OCCURRENCE OF PELVIC VARIATIONS

In this group of 600 white women variations according to the above types occurred as follows:

Dolichopellic type,	92 instances or	15.3 per cent
Mesatipellic type,	272 instances or	45.3 per cent
Brachypellic type,	210 instances or	35.0 per cent
Platypellic type,	26 instances or	4.3 per cent

As in previous reports the mesatipellic or round pelvis predominates (approximately one-half of the series) while the brachypellic or transversely elongated type (oval) occurs in about one-third of the series. This commands interest in view of the fact that until very recently most textbooks held this latter type to be representative of the normal female pelvis. I have discussed certain aspects of this question in an article entitled "What Is a Normal Pelvis?"[4] At this time I may add that from a pragmatic point of view it is reasonable to assume that nature intended the round fetal head (suboccipitobregmatic circumference) to be adapted to a round and not oval-shaped pelvic inlet. In the present communication both the occurrence of variations and the clinical findings associated with the various groups tend to bear out this concept.

It is pertinent to discuss briefly the procedures which we use in a pelvimetric survey of the pelvis:

First: A roentgenogram of the superior strait is made using the so-called "Grid" method.[5] This shows the complete outline of the superior strait and the diameters of this plane may be read directly from the film by means of the corrected centimeter dots appearing on the film. Furthermore, such roentgenograms allow exact reduction of the outline of the superior strait to true centimeters. This record is filed with the prenatal record and is, therefore, immediately available at whatever hour the patient may enter the hospital. These reduced and true images on centimeter paper have a further advantage in that the superior strait is visualized in its true size, not as an enlarged image as it is viewed in the film. In addition this view also allows the mensuration of the important bispinous diameter using a table which corrects for the divergence of the roentgen rays at the level in which these processes rest. This level is ascertained by viewing the lateral film.

Second: A lateral roentgenogram is obtained using a technic described by Thoms and Wilson.[6] In this procedure the patient stands upright with the lateral body plane toward the target at a target film distance of five feet. Resting in the buttocks fold in the midplane of the body is a vertical opaque centimeter notched rod the shadow of which on the film forms a scale for correcting distortion due to the spread of the rays. Views taken in this manner depict all the anteroposterior diameters of the pelvis including the anterior and posterior sagittal diameters of the narrow pelvic plane and the pelvic outlet, the contour and position of the sacrum, and the character of the sacrosciatic notch. This lateral technic used at term or in labor is eminently useful in showing the size and station of the fetal head in its relationship to the bony birth canal. In trial labor this procedure appears to be of exceptional importance.

Third: External pelvimetry of the outlet is done employing the methods described in Williams-Stander and other textbooks.

Emphasis should be made upon the simplicity of the roentgen methods employed. They require but one 10 inch by 12 inch film for each view and, therefore, reduce the cost per patient to a minimum. In appraising the value of roentgen pelvimetric methods in obstetric procedure, the author has recently stated: "The usefulness of the knowledge of the

dimensions of the bony structures of the pelvis and fetus, therefore, has certain limitations, and to draw definite conclusions as to the outcome of labor without considering the whole picture is not only hazardous but unscientific. In other words, the greatly useful knowledge which these roentgen methods have given us must be properly assimilated with our greatest therapeutic weapon, namely, clinical experience.'' I would add that not only the roentgenologist but, since he is responsible for the patient's welfare, the obstetrician should be able to interpret intelligently roentgenograms made for pelvic mensuration.

INCIDENCE OF OPERATIVE INTERVENTION IN THE SERIES

In this series of primiparous patients operative intervention was used in 113 instances. The incidence of operative intervention in relation to pelvic type was as follows:

Dolichopellic type,	15 instances	or 16.3	per cent
Mesatipellic type,	49 instances	or 18.0	per cent
Brachypellic type,	41 instances	or 19.5	per cent
Platypellic type,	8 instances	or 30.7	per cent

The operations are divided as follows:

Cesarean section,	15 instances
Version and extraction,	4 instances
Midforceps,	18 instances
Outlet forceps,	76 instances

The incidence of outlet forceps 76 times in 600 labors should be commented upon inasmuch as many of these patients might have delivered spontaneously if spontaneous birth were an object in itself. It is our belief, however, that in many instances in the primiparous patient when the second stage has been prolonged and the head rests on the perineum, delivery by forceps is often an advisable procedure. The term ''forceps control'' for these cases is a descriptive term and perhaps should be employed.

INCIDENCE OF CESAREAN SECTION ACCORDING TO PELVIC TYPE

Cesarean sections, 15 in number, occurred as follows:

Dolichopellic type	0 instances	or 0	per cent incidence
Mesatipellic type,	2 instances	or 0.7	per cent incidence
Brachypellic type,	9 instances	or 4.3	per cent incidence
Platypellic type,	4 instances	or 15.4	per cent incidence

A brief analysis of these 15 cesarean sections should be of interest and is as follows:

CASE 1.—No. 41108. Small brachypellic type pelvis, 9.5-11.25 cm. Trial of labor followed by cervical cesarean section. Child, 3,050 gm. Lateral roentgenogram during labor showed no attempt at engagement of fetal head.

CASE 2.—No. 64003. Platypellic type pelvis with double promontory, 10.25-13.25 cm. No engagement at term, patient 36 yr. of age. Elective classical cesarean section. Child 3,275 gm.

CASE 3.—No. 21769. Small brachypellic type pelvis, 8.5-11 cm. Rachitic changes in sacrum. Elective classical operation. Child 2,600 gm.

CASE 4.—No. A 36533. Brachypellic type pelvis, 10.25-11.5 cm. Cervical cesarean section after trial of labor. Child 2,995 gm.

CASE 5.—No. A 71000. Brachypellic type pelvis, 10.25-11.5 cm. Unexplained persistent transverse presentation in patient beginning active labor. Classical cesarean section. Child 3,100 gm.

CASE 6.—No. A 73408. Small brachypellic type pelvis, 10.0-12.0 cm. Cervical cesarean section after trial of labor. Child 3,010 gm. Lateral roentgenometry during labor showed no attempt to engage fetal head. Patient of dystrophia dystocia syndrome type.

CASE 7.—No. A 48422. Platypellic type pelvis, 9.25-12.25 cm. Cervical cesarean section after short trial of labor. Child 3,765 gm.

CASE 8.—No. A 48838. Brachypellic type pelvis, 10.25-12.25 cm. Patient with rheumatic heart disease, mitral stenosis. No engagement of fetal head as shown by lateral view at term. Classical cesarean section. Child, 3,250 gm.

CASE 9.—No. A 63078. Small brachypellic type pelvis with narrow forepart, 9.5-11.75 cm. Lateral roentgenogram at term showed no engagement of fetal head and some evidence of disproportion. Cervical cesarean section. Child 2,880 gm.

CASE 10.—No. A 70230. Small brachypellic type pelvis, 9.5-11.5 cm. Trial of labor showed no advance or engagement of head. Cervical cesarean section. Child 2,785 gm.

CASE 11.—No. 60613. Small mesatipellic type pelvis, 10.25-10.5 cm. No attempt at engagement at term in pelvis relatively transversely contracted. Elective cesarean section. Child, 2,950 gm.

CASE 12.—No. A 18087. Average mesatipellic type pelvis, 11.25-12.00 cm. Primary uterine inertia. Irregular and ineffectual contractions over 48-hour period. Lateral view at end of this time showed head high above inlet. Dystrophia dystocia syndrome. Classical cesarean section. Child 3,170 gm.

CASE 13.—No. A 64612. Small brachypellic type pelvis, 10.0-12.0 cm. Lateral at term showed head not engaged. Patient with pregnancy toxemia. Elective cesarean section. Child 3,475 gm.

CASE 14.—No. 39681. Platypellic type pelvis, 9.0-13.0 cm. Elective cesarean section at term for evident disproportion. Child 3,260 gm.

CASE 15.—No. A 56652. Platypellic type pelvis, 9.0-12.75 cm. Evident disproportion at term with large baby. Elective cesarean section. Child 4,290 gm.

COMMENT

In six of the cases of this series, before the section was done a test of labor was given. In our clinic no definite rules govern this procedure. Patients must be carefully individualized and constantly supervised. In this connection the lateral roentgenogram has proved of notable service in reaching a decision between early operative intervention and a prolongation of the test. It is possible that two or three of the patients might have been delivered with difficulty by forceps or by version and extraction. We believe, however, as our knowledge of cephalopelvic relationships increases, that difficult vaginal deliveries, especially in so-called clean cases, will be greatly lessened. The toll of fetal deaths in such operations has received in the past too little attention.

MIDFORCEPS OPERATION

The midforceps operation was resorted to 18 times in the series, an incidence of 3.0 per cent. Most of these operations were done for cases of either high transverse arrest or high persistent occipitoposterior position.

VERSION AND EXTRACTION

Version and extraction was used as a method of delivery 4 times or in 0.66 per cent of the cases. These are briefly summarized as follows:

1. High transverse arrest in average brachypellic type pelvis (11.25-13.5 cm.) after fourteen hours of hard labor, 3,460 gm. child delivered without difficulty.

2. High transverse arrest in small brachypellic type pelvis (10.0-12.0 cm.). A difficult extraction after 22 hours of labor resulting in the stillbirth of a 4,059 gm. fetus. Low cervical section should have been performed (see comment in fetal mortality résumé, Case 9).

3. High transverse arrest in average brachypellic type pelvis (11.5-12.75 cm.) after 22 hours of labor, child, 3,755 gm.

4. Primary uterine inertia, prolonged labor. High arrest. Small mesatipellic type pelvis (10.5-11 cm.). Child 3,350 gm.

FETAL MORTALITY

There were no maternal deaths but there were ten fetal deaths in this series. These are summarized as follows:

CASE 1.—No. A35496. Aged 27 years, average brachypellic type pelvis, 10.75-12.75 cm. Normal spontaneous birth after 22 hr. labor. Fetal heart never heard during labor and fetus showed signs of maceration. Patient's Wassermann and Kahn reactions negative early in pregnancy, but there was later discovered a questionable history of syphilis before marriage.

CASE 2.—No. 57772. Aged 25 years, small brachypellic type pelvis, 10.0-12.0 cm. Low forceps completed a 9½ hour labor. Macerated fetus, fetal heart never heard during labor. Wassermann reaction negative.

CASE 3.—No. A80653. Aged 17 years, average mesatipellic type pelvis, 11.25-12.25 cm. Breech extraction of stillborn hydrocephalic monster with spina bifida. Fetal heart never heard during labor.

CASE 4.—No. 55110. Aged 23 years, small mesatipellic type pelvis, 11.0-11.75 cm. Difficult forceps extraction of stillborn monster with hydrocephalus, spina bifida and club feet.

CASE 5.—No. A51510. Aged 24 years. Average mesatipellic type pelvis, 12.25-13.0 cm. Spontaneous delivery 2755 gm. child which breathed poorly from the first. Respiratory rhythm grew rapidly worse and physical examination showed complete atelectasis on the right. Child died twenty-four hours after birth. Diagnosis: Bilateral pulmonary atelectasis.

CASE 6.—A58171. Aged 20 years, small mesatipellic type pelvis, 10.0-11.0 cm. Labor induced for pre-eclamptic toxemia. Prolonged labor, thirty-two hours, fetal heart not heard toward end of second stage. Low forceps extraction of 2,727 gm. child which could not be resuscitated. Comment: Prolonged labor in toxemia of pregnancy the probable cause of intrauterine death.

CASE 7.—No. 86933. Aged 21 years, average brachypellic type pelvis, 11.0-13.0 cm. Breech extraction of 3,510 gm. child from L. S. A. Duration of labor 22¾ hours. Resuscitation not possible although operation not apparently difficult. Comment: Fetal death probably due to the technic of the procedure.

CASE 8.—No. 68618. Aged 17 years, average mesatipellic type pelvis, 11.5-12.5 cm. Breech extraction of 3,400 gm. child after twenty-eight hours of labor. Comment: Delay in extraction due to extended arms the cause of fetal death.

CASE 9.—No. 93549. Aged 18 years, average brachypellic type pelvis, 11.25-13.0 cm. Twenty-five-hour labor in obese patient with uterine inertia. Midforceps

operation for arrest of labor. Child 3,154 gm., lived two hours. Comment: Operative procedure probably the primary factor in fetal death. Patient of the dystocia dystrophic type.

CASE 10.—No. A44225. Aged 21 years, small brachypellic type pelvis, 10.0-12.0 cm. Version and extraction for arrest of labor after twenty-two hours. Child 4,059 gm., stillborn. Delay in delivering aftercoming head cause of fetal death. Comment: The size of the child should have been recognized and cervical cesarean section performed.

SUMMARY

A total of ten fetal deaths in this series gives a gross fetal mortality of 1.66 per cent for the series. As far as obstetric procedures at the time of labor are concerned, the first five cases showing fetal abnormalities and antepartum death should be eliminated, giving a corrected fetal mortality of 0.82 per cent.

GENERAL CONCLUSIONS

As I have previously pointed out, it appears from this and other studies that we must reconstruct our views with regard to the architecture of the female pelvis. The incidence of the brachypellic type in but one-third of the series makes it appear that this type does not represent the norm in the adult white women of our population. Studies now under way in our clinic on a group of prepubescent girls have shown this type of pelvis to be relatively infrequent. It is our present opinion that environmental influences, especially in early life and during puberty, may be of some significance in determining the configuration of the adult pelvis. In the platypellic group in this series certain sacral changes suggest that rickets probably plays a major rôle as an etiologic factor.

That the dolichopellic and mesatipellic types appear to facilitate spontaneous delivery is further evidenced by the incidence of cesarean section in these two groups, 0.0 per cent and 0.7 per cent, respectively, while in the brachypellic and platypellic types the incidence is 4.3 per cent and 15.4 per cent, respectively. The incidence of operative intervention of all kinds in the series shows the same trend.

The routine use of simple, inexpensive roentgen methods, especially in primiparous women at term, possesses many advantages. Not the least of these is the knowledge we are bound to gain in the treatment of cases of real and suspected disproportion. The use of the lateral roentgenogram during the test of labor makes for scientific accuracy.

Finally, if we are to continue our attack on the problems of maternal and fetal mortality an important objective must be better obstetric care at the time of labor. By making available to the obstetrician exact knowledge of pelvic dimensions we will further reduce the incidence of hit or miss methods in obstetric procedure.

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UTEROSALPINGOGRAPHY WITH SKIODAN ACACIA

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A DEFINITE step forward in gynecologic diagnosis was made by Heuser of Buenos Aires when, in 1921, he made the first injection of iodized oil into the uterus, through the cervix, and thus demonstrated that x-ray studies following this procedure visualized the uterine cavity and the Fallopian tubes. It has now become possible to photograph the normal contour of the uterus and tubes and recognize changes from the normal as to size, position and irregularities of the uterus, and patency or stenosis of the tubes.

Numerous other workers in this field now known as uterosalpingography have added to our knowledge.

Until very recently, iodized oil was the only suitable radio-opaque substance that gave satisfactory results in uterosalpingography. Iodized oil is far from an ideal medium. Reports are continually being published, describing such undesirable and unexpected complications as salpingitis, jaundice, chills and fever, pelvic abscesses, encapsulated oil and foreign body formation in the culdesac and entrance of lipiodal into ovarian and other veins. This has given just cause for hesitation in using iodized oil in uterosalpingography, and has intensified the search for a nonirritating and easily absorbed, nontoxic, radio-opaque liquid, whose use will not be complicated by any untoward results.

Following the report last year of Titus, Tafel, McClellan and Messer on skiodan-acacia (Winthrop), we felt that such a solution should be worth investigating, and if found satisfactory, we would eliminate the disadvantages encountered with the use of iodized oil. We, therefore, present this series of 24 cases in which skiodan-acacia solution was used with the technique that we have developed, and which we feel gives satisfactory pictures and results.

Sodium mono-iodomethane sulphonate (skiodan) in watery solution is entirely nonirritating and noncaustic and has been used extensively, both intravenously and by the retrograde method in urology. It has, however, insufficient viscosity for uterosalpingography. Many combinations with viscid media were attempted to reproduce the viscosity of lipiodal. Skiodan mixtures with starch, dextrose, glycerin, and tragacanth were attempted and rejected as unsuitable. Acacia was finally used and after much animal experimentation with concentrations of acacia from 10 to 40 per cent and skiodan from 10 to 40 per cent in water, saline and dextrose, it was found that aqueous skiodan 40 per cent in 20 per cent acacia was the maximum specific gravity suitable for tubal visualization together with the minimum of

local irritant reaction. Microscopic examination of rabbit uteri, tubes, and peritoneal tissue reveals that the above mixture produces an insignificant inflammatory reaction that has completely healed after twenty-four hours.

This accumulated experience has led to the acceptance of certain basic facts. As a result of all this the following rules should be understood and adhered to in the performance of uterosalpingography:

1. All preliminary gynecologic studies should be completed before uterosalpingography is attempted.

2. This procedure should be done about a week after the patient finishes her menstrual period; as at this time the uterus and tubes are in a quiescent state, and less subject to spasmodic contractions. At this time there is little danger of disturbing a possible early pregnancy.

3. The procedure must not be done in the presence of: (a) an acute or subacute infection of the genital tract, real or suspected; (b) bloody or purulent cervical discharge; (c) temperature, due to any cause.

4. Qualities of the radio-opaque medium: (a) The radio-opaque fluid must be liquid enough for easy injection and yet sufficiently viscid not to escape too quickly after being injected. (b) The fluid must not cause injury nor irritation to the patient's tissues. (c) The fluid must not cause excessive discomfort, pain, or untoward reaction. (d) The fluid should be easily and quickly absorbed into the circulation, and when so absorbed, cause no toxic symptoms or reaction. (e) The radiograph must be clear and brilliant enough to make interpretation of the gynecologic pathology satisfactory.

5. When the x-rays are studied, it must be remembered that the lumen of the tubes does not become distended if the outer end is open, for this permits leakage of the opaque medium into the peritoneal cavity. If the tubes are closed, the solution fills the uterotubal cavity proximal to the point of block and usually gives a clear-cut rounded outline. Abnormalities in the uterine cavity are marked by differences from the normal triangular-shaped uterine cavity.

The test is not meant to supplant the Rubin test (gas insufflation) but to supplement it and thus add additional information.

After some experimentation and modification, the following is the technique that we found to be most satisfactory with this skiodan-acacia solution.

TECHNIQUE

Hospitalization is not required, and no anesthesia is needed. Very nervous or apprehensive patients may be given morphine sulphate gr. ⅙ before starting. The patient voids just before the procedure is carried out.

Instruments used are: vaginal speculum, cervical tenaculum, uterine sound, 20 c.c. Luer syringe, and a uterine cannula that fits the syringe and has a rubber guard that prevents escape of the fluid through the cervix.

The patient is placed in the lithotomy position on a genitourinary roentgen table. The vulva is scrubbed with soap and water and flushed with sterile water; the vaginal speculum is inserted, and the cervix is grasped with the tenaculum and pulled down. The cervix and vagina are swabbed with an aqueous antiseptic. The uterine sound is inserted to determine the depth and direction of the uterus, and also to make the entrance of the uterine cannula easier. The uterine cannula is inserted for a distance of 2 or 3 cm. up to the rubber guard, making a tight fit. The speculum may be left in situ but is better withdrawn. The skiodan-acacia solution, warmed to room temperature, is withdrawn into the 20 c.c. syringe and injected into the uterine cavity through the uterine cannula with slow, gentle, steady

pressure. It has been noted that when 5 or 6 c.c. of the solution has been introduced, the patient will complain of some suprapubic cramplike pains; after several seconds, an attempt is made to gently inject some more solution, and as soon as a definite resistance is felt to the plunger, it may be assumed that the uterine cavity and tubes are well filled. At this point, the first x-ray exposure is made; following this picture, and after waiting for three minutes, it will be found that another 5 c.c. of the solution can be injected, and five minutes after the first film was taken, a second picture is made.

All patients complained of more severe cramps when the skiodan was apparently entering the peritoneal cavity, but this pain was never extreme, nor did it last long. Experience will soon teach one the right amount of pressure to use to obtain the optimum result, without causing injury to closed tubes. It is obvious that the second x-ray picture is invaluable in confirming tubal patency, tubal pathology, or extratubal masses.

After the second film is taken, the syringe and cannula are withdrawn. Some of the skiodan will leak back into the vagina, but enough is retained to give several additional pictures.

Pictures taken thirty to fifty minutes after the injection of the solution show that all of it has already been absorbed and none remains in the peritoneal cavity to become encapsulated or cause further peritoneal irritation.

We present 24 cases selected at random but within the rules mentioned above.

The first six cases may be considered normal controls and in these the uteri were normal in contour, the tubes were patent, and the solution was absorbed rapidly, and no evidence of toxic action was noted.

Cases 10, 11, and 18 were patients with quiescent pelvic inflammatory disease. There was no flare-up of the infection following the use of the skiodan solution. The films showed closed tubes, normal uteri, and the medium was equally rapidly absorbed.

In Cases 16 to 19, we were fortunate in having lipiodal x-ray pictures to compare with the ones we took. Although the lipiodal pictures are somewhat more brilliant, it may be seen that the skiodan shadows are intense enough for an adequate interpretation. Improvement of the x-ray technique with skiodan will help to improve the intensity of the skiodan shadows.

We had hoped, in doing uterosalpingograms with the skiodan solution, that the kidneys might be visualized at the same time. Although several of the pictures suggest a somewhat better visualization of the kidneys than the ordinary flat plate, we must, however, confess our disappointment in the use of skiodan for this purpose, and feel that in these amounts and by this method there is insufficient concentration of the skiodan in the genitourinary tract to give worthwhile shadows.

Patient in Case 20 complained of a slight transient urticaria developing several hours after the injection.

Patient in Case 7 complained of a mild general itch, which also lasted for several hours after the injection.

Both of these manifestations might have been due to sensitivity to acacia.

In the entire group, representing a wide variety of gynecologic conditions, we have experienced no complications of serious import. We feel justified on the basis of our satisfactory results, in recommending the use of skiodan-acacia solution for uterosalpingography with the technique described above for further study and experiment.

TABLE I. REPORT OF CASES

	AGE	CLINICAL DIAGNOSIS	X-RAY FINDINGS
1	24	Normal post partum	Normal uterus; tubes patent
2	28	Normal post partum	Normal uterus; tubes patent
3	26	Normal post partum	Normal uterus; tubes patent
4	36	Normal post partum	Normal uterus; tubes patent
5	26	Normal post partum	Normal uterus; tubes patent
6	28	Normal post partum	Normal uterus; tubes patent
7	35	Left tubo-ovarian mass	Both tubes distended; closed
8	47	Fibroid uterus (submucous)	Normal uterus; tubes patent
9	34	Postoperative salpingectomy	Normal uterus; tubes closed
10	24	Postpuerperal parametritis	Normal uterus; tubes closed
11	26	Chronic pelvic inflammatory disease	Normal uterus; tubes closed
12	31	Primary sterility	Normal uterus; tubes closed
13	36	Fibroid uterus	Large uterus; right tube closed
14	29	Secondary sterility	Normal uterus; tubes closed
15	26	Right oophorectomy, left salpingectomy	Normal uterus; proximal 2 cm. right tube open
16	36	Secondary sterility	Normal uterus; right tube long and narrow; left tube closed
17	24	Left ectopic pregnancy	Normal uterus; right tube patent Proximal 2 cm. of left tube patent
18	35	Bilateral tubo-ovarian disease	Normal uterus; tubes closed
19	35	Right ovarian cyst	Normal uterus; long narrow right tube; normal left tube
20	31	Fibroid uterus	Normal uterus; tubes patent
21	32	Right oophorectomy	Normal uterus; left tube patent Proximal 1 cm. right tube patent
22	36	? Fibroid uterus	Incomplete filling of uterus; tubes closed
23	16	Left ovarian cyst	Normal uterus; long narrow left tube; right tube patent
24	22	Pelvic endometriosis	Normal uterus; tubes patent

SUMMARY AND CONCLUSIONS

1. Twenty-four* cases are presented where radio-opaque aqueous solution of skiodan-acacia (Winthrop) was used for uterosalpingography.

2. In none of the 24 cases were there any untoward results or complications.

3. All cases showed complete absorption of the solution within thirty to fifty minutes.

4. The roentgenograms obtained were sufficiently clear for satisfactory interpretation.

5. Refinement in x-ray technique should give even clearer shadows.

6. This new radio-opaque aqueous solution of skiodan-acacia is recommended for further study as to its use in uterosalpingography.

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*Four cases are from the Gynecological Service of Dr. Edward Davin at the Lincoln Hospital.

THE ROLE OF HYSTERECTOMY IN THE PRODUCTION OF MENOPAUSAL SYMPTOMS

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THE influence of hysterectomy in the production of menopausal symptoms, even when both ovaries are conserved, remains an open question. The many animal experiments dealing with this problem are scarcely applicable to the human being because of differences in anatomic relationships.[1, 2] The studies which have hitherto been reported on the effect of hysterectomy in women are similarly inconclusive because of the associated pelvic pathology.[3-11] In the presence of fibromyomas or pelvic inflammatory disease, for which most of these hysterectomies were done, injury to the ovarian blood supply is a distinct likelihood and if, in such cases, menopausal symptoms later develop it is difficult to know whether they are attributable to the absence of the uterus per se or to an inadequate blood supply to the ovaries. In some of the reported cases, furthermore, the patients were so near the usual age of menopause as to invalidate conclusions. We report the present small series of 42 hysterectomies because they were done, almost without exception, on women who had no demonstrable pelvic pathology and who were still in their reproductive prime. The operations were performed for the sole purpose of sterilization, it being a common practice in this Clinic several years ago to carry out sterilization, when indicated, by means of hysterectomy provided the patient did not wish menstruation to continue. The indications for sterilization in the series are shown in Table I. In order to obviate the age factor, no patient was included in the study who was over 35 at the time of operation, the average age being 29 years. The parity distribution was primiparas 5, secundiparas 6, and other multiparas 31. Twenty-five of the patients were white and 17 colored.

With four exceptions the operations were carried out on patients who were, or had recently been, pregnant. Thus, in 15 cases the hysterectomy was performed immediately after cesarean section; in 16 instances it was done in early pregnancy on the unopened uterus, while in 7 cases, it was carried out one to six weeks after delivery. When done on such pregnant or puerperal uteri, hysterectomy would seem to impose a minimal likelihood of injuring the ovarian blood supply, since the physiologic elongation of the ovarian and infundibulopelvic ligaments makes it possible to clamp, ligate, and sever these structures without encroaching upon the immediate neighborhood of the ovaries. The 42 hysterectomies were done by a number of operators. With the exception of one panhysterectomy, the operations were all supravaginal hysterectomies, but no particular effort was made to leave endometrial tissue. In 36 cases both ovaries were left in situ, but in 6, one ovary was removed along with the uterus.

TABLE I. INDICATIONS FOR STERILIZATION

NO. OF CASES	INDICATION
9	Hypertensive vascular disease
7	Repeated cesarean sections
4	Pulmonary tuberculosis
2	Myomata uteri
1	Pott's disease
1	Acute nephrosis
1	Pyelonephritis
1	Rheumatic heart disease
1	Placenta previa (in a grand multipara)
1	Intrapartum infection (with cephalopelvic disproportion)
14	Psychiatric:
	8 Feeble-mindedness
	4 Jacksonian epilepsy with progressive mental deterioration
	1 Imbecility
	1 Manic depressive psychosis
42	

Following the operation, after periods which varied between 1.6 and 8.0 years, the patients were interviewed in regard to the occurrence of menopausal symptoms. The average interval between the hysterectomy and the interview was 4.1 years. Of the 42 patients, 13, or 30.8 per cent, were followed five years or more; 34, or 80.9 per cent, were followed three years or more; while 41, or 97.6 per cent, were followed two years or more. As shown by Sessums and Murphy, if a patient is going to develop menopausal symptoms after hysterectomy, these become manifest within the first two years in over 90 per cent of cases and within three years in 95 per cent. Each patient was questioned in person in regard to the various signs and symptoms of the menopause, including hot and cold flushes, sweating, headache and vertigo, libido, indigestion, psychic and nervous disturbances, and weight gain. However, with the exception of hot flushes the symptoms were often so vague that it seemed best to evaluate the cases on the basis of hot flushes only. The term, menopausal symptoms, in this paper therefore, refers only to hot flushes. Sessums and Murphy used the same criterion.

TABLE II. THE INCIDENCE OF PHYSIOLOGICAL MENOPAUSE DEVELOPING IN WOMEN UNDER FORTY COMPARED WITH THE INCIDENCE OF SURGICAL MENOPAUSE FOLLOWING HYSTERECTOMY WITH OVARIAN CONSERVATION

CONDITION	SOURCE	NUMBER OF CASES	PERCENTAGE DEVELOPING SYMPTOMS
Hysterectomy done on normal pregnant and puerperal women before the age of 36 with symptoms developing before the age of 40	Present series	42	16.6
Physiologic menopause	Norris	200	1.5
	Novak	100	3.0
	Sanes	567	7.77
Hysterectomy done on women menstruating regularly but irrespective of age	Mandel and Bürger	96	67.7
	Peterson	27	74.0
	Graves	26	81.0
Hysterectomy done before the age of 37	Kretzschmar and Gardiner	64	57.8
Hysterectomy done before the age of 36 with symptoms appearing before 40	Sessums and Murphy	91	43.9

The results of the present study may be seen in Table II, together with figures culled from the literature, showing (a) the incidence of menopausal symptoms developing in women under forty who have not been subjected to operation and (b) the incidence of menopausal symptoms following hysterectomy with ovarian conservation.

It is apparent that the incidence of menopausal symptoms in our series, namely, 16.6 per cent, was decidedly less than that hitherto reported in the literature, that is, 43.9 to 81.0 per cent. In other words, when hysterectomy is performed on the pregnant or the puerperal uterus in the absence of pelvic pathology, it is much less likely to produce menopausal sequelae than when done in the presence of fibromyomas and pelvic inflammatory disease. While this circumstance may be subject to several interpretations, it would seem most plausibly explained by the greater technical difficulties of hysterectomy in the presence of pelvic pathology and the greater likelihood of injuring the ovarian blood supply. If this fact be true, it suggests that hysterectomy with ovarian conservation brings about menopausal symptoms through injuring the ovarian blood supply rather than through the absence of the uterus per se.

The writer wishes to acknowledge the assistance given by Dr. Marion Fairfield, now of Nashua, New Hampshire, in interviewing the patients.

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Simpson, S. Levy, and Joll, Cecil A.: Feminization in a Male Adult With Carcinoma of the Adrenal Cortex, Endocrinology **22**: 604, 1938.

A case of feminization of a male aged 34 is described, together with the partial remission of symptoms following removal of an adrenal carcinoma. Death subsequently followed the recurrence of growth and metastases. The patient excreted a considerable excess of estrogenic hormone (probably estrone), which disappeared after operation and returned with the recurrence of the growth. The histologic picture showed certain differences from that of an adrenal carcinoma removed from a virile woman, who secreted an excess of comb-growth hormone. The histologic differences may explain why, in the one case, estrogenic hormone and, in the other case, comb-growth hormone were excreted. The clinical and biologic evidence suggests that the adrenal tumor was directly or indirectly responsible for the excess of estrogenic hormone found in this case of feminization. A similar hypothesis was advanced in a previous paper for the presence of an excess of comb-growth hormone in the urine of virile women.

J. Thornwell Witherspoon.

ENDOMETRIOSIS IN LAPAROTOMY SCARS

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ALTHOUGH endometriosis in laparotomy scars may no longer be considered rare, the condition is seen infrequently enough to warrant reports of new cases. It was these nodules in a scar following cesarean section which helped form the basis of Sampson's theory of transtubal implantation, which has had such widespread influence in stimulating interest in the general subject of endometriosis.

In 1920 Mahle and MacCarty[2] reported 2 cases, following ventral suspension of the uterus and shortening of the round ligaments, respectively. They were unable to demonstrate a direct fistulous communication between the uterus and abdominal wall, nor were Nicholson[3] or Lemon and Mahle,[4] in their respective reports of 32 and 9 cases. Heaney[5] cites 29 cases in 1925, adding 2 of his own, while Danforth[6] reported an additional case at the same time. In 1928 Mason and Simon[7] reported 16 cases in a paper on uterine fistula and suggested the injection of radio-opaque media as an aid in diagnosis, the injection of methylene blue also being suggested at a later date by Keene and Kimbrough.[8] The same year, Ballin[9] collected 40 cases which he considered as direct communications between the uterus and tubes and abdominal wall. Many other cases have been reported recently.[10-12]

The type of operation preceding these lesions varies considerably, but operations upon the tubes, round ligaments, ventral suspensions, and cesarean sections head the list, although the operation may be extrapelvic, as demonstrated by a recent case[13] of endometriosis in the scar following operation for a strangulated inguinal hernia and several cases following appendectomies.[1, 7]

M. H., colored, aged 37 years, was admitted to the University Hospital June 6, 1937, with the chief complaint of pain and bleeding in an abdominal scar. Twenty years previously she had had an appendectomy and bilateral salpingectomy for acute appendicitis and acute salpingitis. The past history and family history were nonessential. The general history was negative except for bleeding from the rectum during the present illness. There was no hematuria. Her menses were of the 13-28-4 variety. Leucorrhea had been present for twenty years. The last menstrual period was May 18, 1937, the previous menstrual period was April 16, 1937.

The present illness began in 1935, or eighteen years after the original operation, with pain in the incision and right lower quadrant during the catamenia, beginning one week before its onset and lasting three to seven days after. In May, 1937 a small nodule was noticed in the incision which bled a little each day, but more profusely during menstruation.

The general examination showed a poorly developed colored woman. The breasts were normal. The abdomen showed a low midline scar with a small, indurated area in the middle which bled easily. The vulva, vagina, and cervix were essentially normal. There was no induration of the rectovaginal septum. The uterus was small, attached to the abdominal wall and fixed. There was a firm, smooth mass about 6 cm. in diameter in the left adnexal region which moved with the uterus.

Proctoscopic and cystoscopic examinations unfortunately were not made. The urine was negative. The Kolmer and Kahn tests were positive. R.B.C., 3,610,000; Hb., 65 per cent; W.B.C., 6,850.

On June 9, 1937, under gas-oxygen-ether anesthesia, a laparotomy was performed; incision was made to include the old scar. Near the middle of the incision, above the fascia, a blood-filled cyst was encountered. The right uterine cornu and right ovary were densely adherent to the peritoneal scar, a pedunculated uterine myoma was found arising on the left. A supravaginal hysterectomy and bilateral oophorectomy were performed.

Pathologic examination showed no true fistula. The scar (Fig. 1) contained numerous areas of endometriosis. The right ovary and myometrium showed an occasional endometrial gland.

The postoperative course was uneventful and the follow-up has shown the patient to be in good condition with no complaints.

The objective and subjective symptoms of this case are typical, as are the operative and pathologic findings. For these cases the operative morbidity and mortality rates are very low, the results excellent, often ovarian conservation being possible. The long latent period in this and other cases is difficult to correlate with Sampson's theorem, for it seems unlikely that transplanted endometrium could remain dormant

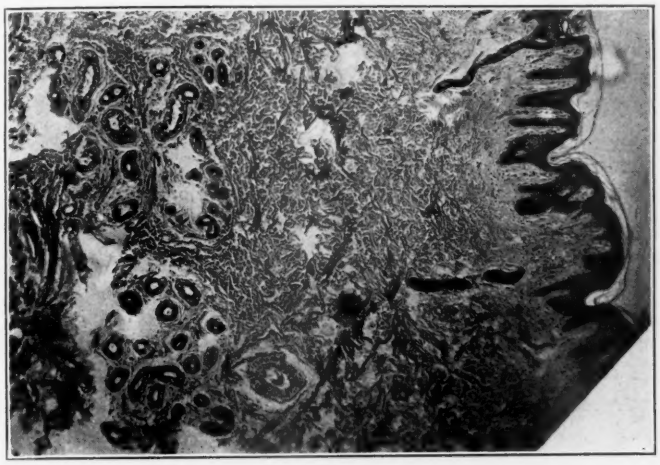

Fig. 1.—Section of abdominal scar showing numerous endometrial glands.

for a period of twenty years, suddenly springing into activity. One is forced to admit that, despite the large amount of work devoted to this subject, we have not yet arrived at a theory which explains every case of endometriosis.

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Barker, Robert H.: The Placental Transfer of Sulfanilamide, New England J. M. **219:** 41, 1938.

Sulfanilamide given to pregnant women shortly before or during labor is absorbed in the gastrointestinal tract and passes readily through the placenta to the fetus to appear in almost equal concentrations in maternal and fetal venous bloods.

Hugo Ehrenfest.

ENDOMETRIAL PATTERNS IN DYSMENORRHEA

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IN A RECENT paper[1] we have presented the findings in a series of cases of functional dysmenorrhea which demonstrated that a large percentage of such cases had a high blood and urine level of the follicular hormone throughout the menstrual cycle. We had at that time no clinical method of determining the quality or physiologic activity of the luteal hormone. But, from the concept of the interrelationship of the two hormones, it seemed probable that such high levels of the follicular hormone would be accompanied by deficiencies of the luteal hormone, and that since theelin increases uterine contractions, the presence of excessive or unbalanced quantities of this substance might account for the pain incident to menstruation.

The introduction of the endometrial biopsy has given us a method by which the physiologic activity of the corpus luteum may be judged. From cases so studied we wish to present the findings in 50 cases of functional dysmenorrhea.

The cases selected for study were those whose main, but not necessarily only complaint, was dysmenorrhea and in whom there were no gross systemic or pelvic abnormalities. The study of each case included a general and pelvic examination, blood count, urinalysis, Kahn, basal metabolic rate, premenstrual blood hormone determinations according to the Frank-Goldberger technique, and premenstrual endometrial biopsies.

There is no universally accepted classification of the endometrial changes during a menstrual cycle. Sturgis and Meigs[2] have classified the cyclic changes as consisting of two phases, the proliferative and the secretory, corresponding to the periods of function of the Graafian follicle and the corpus luteum, respectively.

Herrell and Broders[3] have used the terms proliferative and differentiative to apply to the same phases. They have further called attention to the fact that in some cases of menstrual abnormalities, the endometrium does not complete its cycle of growth and differentiation, which results in persistent phases of the cycle and that such endometrial patterns indicate the type and degree of ovarian failure. Randall and Herrell[4] have further pointed out that besides the types of endometria in which arrest of the development is the only finding significant of ovarian failure, there may also be cystic changes in the endometrium as the result of an abnormality of hormone balance in either phase. They also point out that the idea that the corpus luteum functions in an "all or none" manner is erroneous. Glandular cystic hyperplasia in a secretory endometrium indicates that ovulaton may have occurred but that a normally functioning corpus luteum has not followed.

The findings in the endometrial biopsies in the cases studied fell into the following groups: Normal secretory or differentiative reactions, 18 cases; secretory or differentiative with cystic changes, 9 cases; per-

sistent late proliferative phase, 10 cases; persistent early proliferative phase, 2 cases; proliferative cystic hyperplasia, 11 cases.

In the cases with normal secretory function, eleven had no other complaints, one had polymenorrhea, and three oligomenorrhea. The basal metabolic rate was within normal limits in all except four cases. The outstanding finding in this group was the occurrence of pelvic congestion in 10 cases. In all cases but two there was at least a normal amount of the estrogenic hormone in the blood premenstrually.

Secretory or differentiative changes with cystic hyperplasia occurred in 9 cases. Of these, there was one case each of oligomenorrhea and polymenorrhea. The uterus was infantile in type in 3 cases and retroverted with pelvic congestion in 1. The basal metabolic rates were below normal in all except 2 which were within normal limits. Estro-

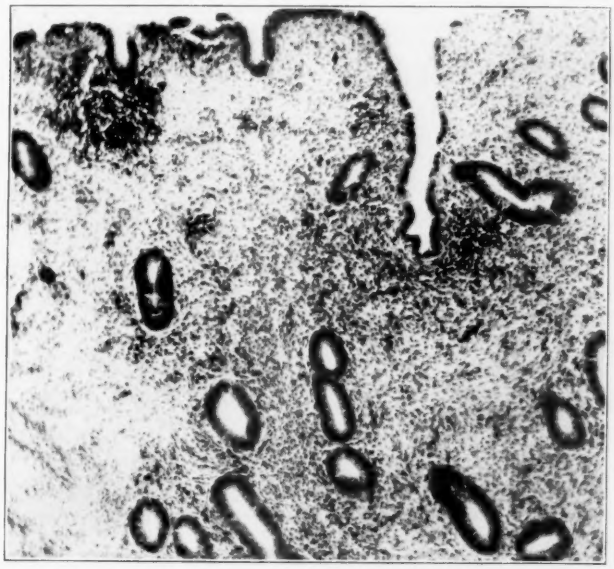

Fig. 1.—Persistent proliferative (follicular) phase. A married woman aged 30 years, whose chief complaint was severe dysmenorrhea with prolonged flow and clots since resection of both ovaries seven years ago. Biopsy taken twenty-seven days after onset of previous period and menstruation followed one day later, lasting twenty days. Premenstrual blood hormone tests: Very strong positive estrogenic (Frank-Goldberger technique), reaction I gonadotropic (Zondek technique), basal metabolic rate minus 12.

genic substance was demonstrable in all except 3. Gonadotropic substance was present in only 1 case.

Arrest of the endometrium in the proliferative phase occurred in 23 cases in 11 of which cystic hyperplasia was also present. Estrogenic substance was demonstrable in 14 cases and absent in 9, 2 of the latter group having positive gonadotropic hormone tests. The uterus was normal in all cases except one which was infantile in type and one retroverted. There were 3 cases of pelvic congestion. The basal metabolic rate was practically normal in all cases. This group included 4 cases of polymenorrhea, 4 of oligomenorrhea, and 2 of mammary hyperplasia.

Anemia was a common but significant finding in all of the cases. There was a tendency for the basal metabolic rate to be low, 15 being below minus 10, 30 within normal limits, and 5 above plus 10. It is interesting to note that the group in which the basal rate was consistently low was that in which there was a cystic secretory phase of the endometrium. Urinalyses were negative in all cases as were the Kahn tests. Associated menstrual abnormalities were present in 15 cases with a tendency for these to occur when the endometrium was of an abnormal type.

In seeking to determine the endocrine status on the basis of the endometrial picture, we interpret that of the 50 cases of functional dysmenorrhea, there were 27 in which ovulation had occurred but in only 18 of these was ovulation followed by normal corpus luteum

Fig. 2.—Cystic proliferative (follicular) phase. A married woman, aged 28, whose chief complaints were dysmenorrhea and hypomenorrhea and sterility. Biopsy taken twenty-seven days after onset of preceding period and menstruation followed six days later, lasting seven days. Premenstrual blood estrogenic substance positive, gonadotropic negative, basal metabolic rate minus 13.

function. All of these 27 apparently had adequate and 9, excessive follicular activity. Twenty-three of the 50 apparently had no corpus luteum at all; but of these, 21 had follicular function and 11 in excessive amounts. It seems probable, therefore, that in 18 there was a normal balance between the follicular-corpus luteum function and in 30 there was follicular function present but unbalanced by corpus luteum function. In only 2 cases was there a deficiency of both functions.

The endometrial biopsy gives a more accurate estimation of the physiologic activity of the ovarian hormones than bio-assay of the blood and urine for the hormone content, because the endometrium reflects the extent to which the hormones are physiologically effective, whereas

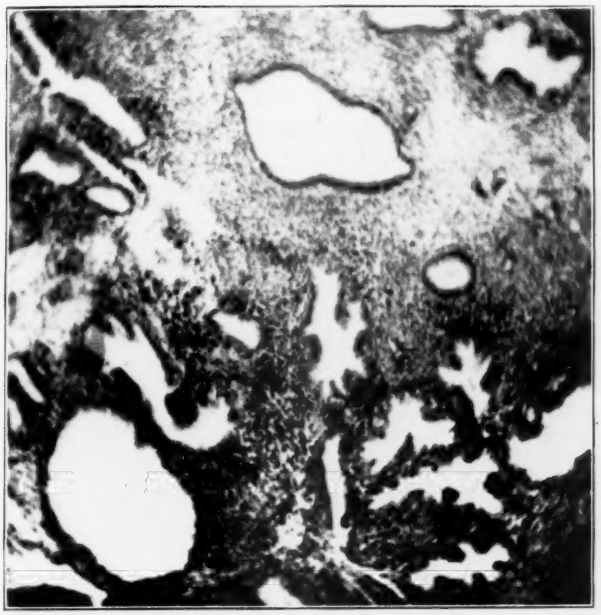

Fig. 3.—Secretory (differentiative) phase with cystic changes. A married woman, aged 25 years, whose only complaint was severe dysmenorrhea since beginning of menstrual function. Biopsy taken twenty-eight days after onset of previous period and menstruation started immediately thereafter. Blood estrogenic substance, strong positive; gonadotropic negative.

Fig. 4.—Secretory (differentiative) phase. An unmarried woman, aged 21, whose only complaint was severe dysmenorrhea. Biopsy taken twenty-four days after previous period and menstruation followed six days later. Blood estrogenic substance, positive, gonadotropic, negative, basal metabolic rate, minus 4.

titration merely gives an estimate of the amount present at a given time and tells nothing of how efficient it is in the organism. It must be remembered, however, that there are occasions in which the ovary may be normal in function but the uterus unresponsive.

Menstrual disorders cannot be classified by symptoms. In reviewing this small series of cases we find that each type of abnormality of the menstrual flow may occur with any type of endometrium. Amenorrhea was of course not included. Dysmenorrhea is a symptom and must be treated as such. Each case must be investigated fully if any hope of success is to be realized. To give a patient with negative physical findings hormone therapy on the presumption that there is a glandular dysfunction will lead to negative results in many cases. Pelvic congestion, as demonstrated in this series, is an important factor in the production of many of the gynecologic symptoms. It is usually the result of improper sex hygiene. It apparently was the underlying cause of pain in 13 of the otherwise normal individuals in this series of cases. Even when all factors have been thoroughly investigated there still remains a small group of cases in which no positive findings are present to account for the pain.

SUMMARY

1. Fifty cases of functional dysmenorrhea were studied with especial emphasis placed on the findings from endometrial biopsies.

2. Of the 50 cases, 18, or 36 per cent, had normal endocrine function and 32, or 64 per cent, had some degree of ovarian failure. Of these failures, 30, or 60 per cent, were primarily corpus luteum deficiencies; 20, or 40 per cent, showed associated excessive follicular activity. Only 2, or 4 per cent, showed deficiency of both hormones.

3. Of the cases within normal hormone balance, 10, or 20 per cent, had pelvic congestion present as a possible etiologic factor.

4. In 8, or 16 per cent, there was nothing to account for the dysmenorrhea.

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Bowles, H. E.: The Graefenberg Ring. Its Use and Abuse With a Case Report, Japanese J. Obst. & Gynec. **21:** 2, 1938.

The author emphasizes that a foreign body in the uterus may produce irritation and inflammatory changes in the uterus and adnexa. Accidents from the use of intrauterine pessaries have been reported from various parts of the world and the author reports an additional one. He comes to the conclusion that the Graefenberg contraceptive ring should be abandoned in favor of safer contraceptive measures.

J. P. Greenhill.

THE EFFECT OF PREGNANCY AND THE CORPUS LUTEUM UPON VESICAL MUSCLE*

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THE innervation of vesical muscle has been studied in this laboratory for several years. It became obvious in the course of the experiments that there were factors other than the nervous stimuli to be considered as influencing vesical activity. We early began to exclude pregnant cats from our series of experimental preparations. The bladder appeared to be capable of holding an unusually large volume of fluid at low pressures. This increased capacity was still present for days or weeks after pregnancy was terminated. The conclusion was reached that the vesical muscle was influenced in its capacity not alone by its nerve supply but also by chemical substances carried in the blood.

It has been known for many years that changes in the urinary tract take place with pregnancy. These have been studied particularly in the ureters but have a direct relation to the present experiments. In 1843 Cruveilhier first described dilatation and elongation of the ureter as a frequent accompaniment of the gravid state. He believed that there was a hyperplasia of the tissues composing the walls of the kidney pelvis, the ureter, and the bladder in the form of increased thickness of the muscular and connective tissue elements. In spite of this hypertrophy the lumen of the ureter is dilated. The extent to which these changes appeared varied much in different individuals as well as in the ureters of the same individual, the process usually being more marked on the right side.

Two explanations for these phenomena have arisen. One group has felt that the pressure of the enlarged uterus upon the ureter at the point where it crosses the pelvic brim was the chief factor. However, larger pelvic tumors than those represented by the pregnant uterus were not often productive of the ureteral changes in the nonpregnant patient. Other authors have suggested an atony of the ureteral musculature. Dilatation of the ureter usually reaches its maximum at about the seventh month of pregnancy, and frequently diminishes toward term despite the enlargement and increasing weight of the uterus.

Traut and McLane (1936) studied contraction waves in the ureters of their patients. The normal ureter of the nonpregnant woman is possessed of rhythmic peristaltic activity which can be measured and recorded. In the majority of patients this rhythmic activity is definitely changed in pregnancy in varying degrees. The altered peristaltic activity is expressed by diminished amplitude of the peristaltic wave commencing in the third month of pregnancy but reaching its peak during the

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seventh and eight months. After the fifth month the number of patients showing diminished ureteral response exceeds those showing normal activity. During the last month of pregnancy there seems to be a definite return of muscular irritability as expressed by the measurement of peristalsis and response to stimulation. This diminished peristaltic activity of the ureters seen in pregnancy cannot be explained on the basis of dilatation. On the contrary, dilatation of the ureters during pregnancy is probably in great part dependent upon the atony of the ureters. The etiology of this ureteral atony during pregnancy is, in the opinion of the authors, not due to any mechanical factor but rather has some, as yet unexplained, chemical basis.

Later Traut, McLane and Kuder (1937) pointed out that the characteristics of the ureteral atony are similar in many respects to those affecting the uterine musculature. It was suggested that the phenomena in the two organs may have a similar etiology. The ureteral dilatation is roughly proportional to the degree of atony, and both appear and disappear at similar times with regard to the course of pregnancy. Dilatation and atony appear in the third month and are progressive to the seventh month of pregnancy. During the last two months there is a marked increase in motility, accompanied by a moderate decrease in the dimensions of the tract. Following delivery atony is again marked until the third week, subsequent to which motility returns rapidly to normal levels, which are usually attained during the sixth and seventh weeks post partum. Dilatation of the tract decreases progressively after delivery and reaches practically the normal values at the seventh week of the puerperium.

Hundley, Walton, Hibbitts, Siegel and Brack (1935) felt that the atony of the ureter must be the result of the activity of hormones elaborated during pregnancy. They found hypertrophy of the muscle, edema, and increased vascularity in the whole urinary tract.

Other experiments more closely related to the bladder have been performed by Woolsey and Brooks (1937). They placed cats for long periods in metabolism cages equipped with apparatus for recording continually volume and time of micturition. Micturition volume diminished markedly during estrus or while the animal, female or male, was under the influence of progynon-B. In the female the decrease was correlated with the vaginal smear and estrous cycle. Tremendous increases in micturition volume were observed post partum.

METHODS

The experiments involved considerable technical difficulties. We chose to use rabbits since corpora lutea can be produced in these animals very easily. This animal normally ovulates only at the time of copulation. Injection of antuitrin-S also produces ovulation in the rabbit. Previously the cat has been employed almost exclusively for our studies of vesical function.

Catheterization of the urethra in the rabbit is difficult because the urethral meatus is well up in the vagina. However it was found possible to introduce a fine glass catheter through the urethra into the bladder of the rabbit and make readings of vesical activity after the same manner which has been employed in cats. The animals were always anesthetized with pentobarbital injected intravenously. Before any further procedures were instituted three control readings at ten-day intervals were made to learn the average vesical capacity of the animals. If these readings showed little variation, the experiment was continued.

In this work we used as the criteria of the experiment any changes from the normal vesical capacity which occurred during pregnancy and following ovulation. Records were made of intravesical pressure during filling of the bladder; the pressure remained low until the viscus was reaching the limits of its capacity. The normal vesical capacity of an animal under deep anesthesia is remarkably constant as the readings show. Under pentobarbital anesthesia the vesical muscle does not contract reflexly (Kolb and Langworthy, 1938), and urine escapes only by overflow

when the intravesical pressure is slowly raised to a point which is rather constant for the individual. The vesical volume was increased by adding 2 c.c. of fluid at a time until this overflow occurred. Between each introduction of fluid the intravesical pressure was allowed to fall to a resting level. We felt that a demonstration of increased vesical volume developing coincidently with pregnancy suggested an atony of the vesical musculature such as has been shown for the ureters by Traut.

The rabbits did not stand the repeated administration of an anesthetic well and many were lost during the course of the experiments. For the same reason pregnancy was not often carried to its termination. The edema of the vagina and vulva subsequent to ovulation and during pregnancy was an obstacle to successful catheterization of the urethra.

A few animals developed intractable diarrhea with loss of weight. During the period of diarrhea the vesical volume was increased. Careful records of the weight of the animals were kept from week to week. If a rabbit was losing weight, it was dropped temporarily from the experiment. In general the changes in weight had no correlation with the results. The weights are recorded in the control series shown in Table I.

TABLE I. CASTRATED RABBITS

EXP.	FIRST READING		10-DAY INTERVAL		10-DAY INTERVAL			10-DAY INTERVAL	
	VOL.	WT.	VOL.	WT.	VOL.	WT.		VOL.	WT.
1	8	4.5	24	5.0	12	5.5	Antuitrin-S	18	5.25
2	14	6.0	24	6.75	24	6.75		14	6.5
3	26	5.5	38	6.0	44	6.0		20	6.25
4	16	6.5	22	7.0	10	6.5		14	5.25
5	26	6.0	18	6.5	22	6.5		26	6.75
6	26	5.0	8	5.25	10	5.5		6	5.0
7	48	7.0	26	8.0	26	6.25		18	5.75
8	20	4.75	38	6.0	20	6.25		32	5.75
9	40	3.5	14	4.25	20	5.25		26	5.5
10	30	4.5	20	5.25	32	6.0		30	5.75

EXPERIMENTAL OBSERVATIONS

A. Table I shows the results of a study of ten control animals. The ovaries were removed from the young adult rabbits and they were allowed to recover from the operations. Subsequently a series of four readings of vesical volume was made upon each rabbit at ten-day intervals. After the first three readings the animals were each given 0.2 c.c. of antuitrin-S intravenously. The weight of the rabbit at the time of each reading is given in the chart. According to Dr. Franklin Synder this is sufficient hormone to produce ovulation. It will be observed that the rabbits tended to gain in weight during the progress of the experiment. The readings of vesical volume show only slight variations; ten days after the injection of antuitrin-S no significant changes in vesical volume appeared.

B. The changes in vesical volume associated with pregnancy are shown in Table II. All the rabbits used in the experiments were young virgin females. The records are not complete in all the cases due to difficulty in keeping the rabbits alive and in catheterizing the bladder during pregnancy.

The three control vesical readings are relatively constant for the single individuals. After the third reading the animal was placed with a male. The next reading was made ten days later. Where pregnancy ensued there was in every case an increase in the vesical volume. The normal volume was in several instances doubled or tripled.

Inasmuch as the period of gestation in the rabbit is thirty days it was sometimes possible to make three readings during the period of pregnancy; the results are shown in the tables. As the uterus increased in size there was in certain cases a diminution in the vesical capacity, although the capacity was still much greater than in the nonpregnant animal. Perhaps this was due to mechanical factors pro-

TABLE II. EFFECT OF PREGNANCY. CONTROL READINGS

EXP. NO.	1ST CONTROL	10 DAYS LATER	20 DAYS LATER		30 DAYS LATER	40 DAYS LATER	50 DAYS LATER	10 DAYS FOLLOWING DELIVERY
1	22	26	18		76			
2	32	28	26		50	56		
3	22	22	24		38			
4	14	26	24		30	40	34	
5	26	28	26		40	40	46	
6	14	14	14		26	56	34	
7	10	16	12		36	36	50	70
8	18	12	16		26	34		
9	28	22	16		36	34	46	60
10	18	14	16		40	32	34	58
11	28	28	32		68	34	58	60
12	24	22	20		54	36	42	66
13	8	4	10		30	24	28	58
14	14	8	12		26	28	22	38
15	22	24	18		50	58		
16	18	16	14		34	24	28	
17	36	22	36		56			

Rabbit placed with male.

duced by the pressure of the gravid uterus. In other cases the bladder capacity continued to increase through the period of pregnancy.

Following the termination of pregnancy the vesical volume was greater than at any previous period. It appeared that the bladder was free from any pressure from the uterus and could expand to the limits of its capacity. The bladder remained of large volume for three or four weeks following the termination of pregnancy, and it was only at the end of this time that it returned to its normal volume.

C. The final series of experiments had to do with the production of ovulation in the normal rabbit by the injection of antuitrin-S. This group was the most difficult to carry out satisfactorily and the least conclusive. Ovulation did not take place in every case and it was necessary to open the abdomen and make sure of the condition of the ovaries. When ovulation occurred, edema of the vulva and vagina often defeated catheterization. The bladder showed its greatest increase ten days after the injection of antuitrin-S. It may be said that the vesical volume was increased in approximately 50 per cent of the cases. The changes when they did occur were large enough to seem to us significant. They are given in Table III.

TABLE III. PRODUCTION OF OVULATION BY INJECTION OF ANTUITRIN-S IN NORMAL RABBITS

	FIRST CONTROL	SECOND CONTROL 10 DAYS LATER	THIRD CONTROL 20 DAYS LATER		30 DAYS LATER
1	12	12	18		30
2	14	18	16		26
3	18	12	16		34
4	14	14	14		44
5	12	8	14		30
6	14	12	20		28
7	12	14	20		30
8	18	14	12		38
9	8	10	8		24
10	14	20	20		44
11	16	28	14		40
12	12	16	12		36
13	16	14	10		38
14	18	28	18		54
15	18	8	12		28

Antuitrin-S

DISCUSSION

We have noticed repeatedly in pregnant cats or in animals which had recently been pregnant that the bladder is capable of holding an unusually large quantity of urine so that these animals are not suitable for studies of disturbances of vesical innervation. In the present experiments we have endeavored to put to a test the effect of pregnancy upon the vesical capacity. When the readings were made the rabbits were deeply anesthetized so that the stretch reflex was no longer active, and fluid escaped only by overflow when the organ had reached the limits of its capacity. By three control readings at ten-day intervals in the normal animals we have demonstrated that the vesical capacity remains relatively constant. Ten days after the animals had been with the male and thereafter through pregnancy and the puerperium the vesical volume was increased.

The relationship of the increased vesical volume to changes in the bladder muscle is not established. It seems reasonable to assume that the increased volume is dependent upon decreased tone in the muscle. Microscopic study of the vesical muscle in six animals revealed no significant changes.

The question then arose as to whether ovulation produced similar changes. In ovariectomized rabbits the injection of antuitrin-S had no effect upon vesical capacity. It is therefore reasonable to assume that the anterior pituitary-like sex hormone itself has no direct effect on the bladder muscle. Approximately one-half of the adult virgin rabbits showed a significant increase in vesical volume ten days after the injection of antuitrin-S. These results lead us to assume that a substance is elaborated by the corpus luteum which causes a decrease of tone in the vesical muscle. We are not prepared at the present time to hazard an opinion as to which of the corpus luteum hormones, estrin or progestin, this effect on the bladder muscle tone is due.

These findings are similar to the changes reported in the ureters in women during pregnancy. They make it appear likely that similar changes occur throughout the length of the urinary tract.

Our findings of increased vesical volume following pregnancy confirm the experiments of Woolsey and Brooks. Their results were obtained by quite a different technique. Their findings of diminished volume during estrus or under the influence of progynon-B also lead to the assumption that the sex hormones influence bladder musculature. The fact that progynon-B caused a decrease in bladder capacity suggests that the increased capacity noted by us during pregnancy is due to progesterone rather than estrin.

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HEMATOMETRA

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HEMATOMETRA is due either to congenital or acquired atresia. Blood retention incidental to menstruation or other bleeding produces distention of the vagina (hematocolpos), uterus (hematometra), and Fallopian tubes (hematosalpinx). Hematovarium and hematoperitoneum also occur.

Since the subject is briefly described in most textbooks and only occasionally referred to in the literature it merits presentation. The interesting pathologic and etiologic aspects, as well as its clinical significance, are discussed on the basis of a group of 19 cases. These represent an incidence of 0.1 per cent of all gynecologic admissions to Mount Sinai Hospital during the years between 1917 and 1937.

In this group, congenital causes of the disease predominate; namely imperforate hymen (10 instances), and bicornuate uterus (1 instance).

CONGENITAL STENOSIS CAUSING HEMATOMETRA

A. *Imperforate Hymen (10 Cases).*—

CASE 1.—Hematocolpos, hematometra, right hematosalpinx.

This 15-year-old patient complained of dysuria for a year. In addition she had backache and abdominal enlargement for one month. Pelvic examination disclosed a blue, bulging, imperforate hymen, and a cystic pelvic mass reaching to the navel. The hymen was excised and the postoperative course was uneventful.

CASE 2.—Hematocolpos and hematometra.

For one year this 16-year-old patient complained of periodic backache. An imperforate bulging hymen and a soft cystic uterus the size of an eight months' gravidity were found. The hymen was excised and trocar drainage instituted.

CASE 3.—Hematocolpos and hematometra.

This 13-year-old patient had backache for eighteen months. For ten days before admission, there was difficulty in voiding. The hymen was imperforate and a cystic uterus of six months' gravidity size was palpable. The pelvic organs returned gradually to normal size after the hymen was excised and the retained blood drained.

CASE 4.—Hematocolpos, hematometra, and hematosalpinx.

Hypogastric distress for two weeks was the only symptom of this 14-year-old girl. There was right rectus spasm and rigidity. The hymen was imperforate, bulging and cyanotic. The uterus reached the umbilicus. A soft mass filled the cul-de-sac. In this case a satisfactory result was obtained after excising the hymen.

CASE 5.—Hematocolpos and hematometra.

The chief complaint of this 17-year-old girl was periodic lower abdominal pain for one year. The hymen was imperforate and bulging; the soft uterus reached to the umbilicus. The hymen was excised and the uterus drained with a hard rubber tube. The uterus contracted immediately to normal state.

CASE 6.—Hematocolpos.

The history of this 15-year-old girl revealed a vaginitis of four years' duration. Because of inability to void she had been repeatedly catheterized for the month before admission. The hymen was cyanotic and bulging but the uterus was not enlarged. Cure was obtained by excision of the hymen.

CASE 7.—Hematocolpos and hematometra.

Since a hymenoplasty, two years before admission, this 16-year-old girl had intermittent backache. The hymen was cyanotic and bulging. The uterus reached to one inch above the umbilicus. Excision of the hymen produced a cure.

CASE 8.—Hematocolpos and hematometra.

This 13-year-old girl complained of sticking pain in the right lower quadrant of six months' duration, and of continuous lower abdominal pain of two weeks' duration. The hymen was imperforate and the uterus reached to within three fingerbreadths of the umbilicus. Culture of the retained vaginal blood was sterile. The operation was needle aspiration followed by an excision of the hymen.

CASE 9.—Hematocolpos and hematometra.

This 12-year-old girl complained of lower abdominal pain and urinary incontinence of four days' duration. The hymen was bulging and imperforate and the uterus reached to within three fingerbreadths of the umbilicus. The operation consisted of trocar drainage followed by hymenectomy five days later.

CASE 10.—Hematocolpos and hematometra.

This 14-year-old girl complained of backache and intermittent paraumbilical pain of three months' duration. The hymen was bulging and imperforate, the soft uterus reached to within three fingerbreadths of the umbilicus and was asymmetrical. The latter observation suggested the possibility of a hematosalpinx. The operation was hymenectomy.

B. *Bicornuate Uterus.*—

CASE 11.—Uterus bicornis unicollis with ovarian endometriosis.

This 27-year-old nulligravida was married for seven years; and complained of dysmenorrhea, dyspareunia, and continuous pain in the left lower quadrant which increased in severity during the menses. The menstrual cycle was otherwise normal. Pelvic examination disclosed a one finger nulliparous introitus with marked vaginismus. The uterus was enlarged and bilobed and a tender mass arising from its left tubal angle was fixed to the lateral pelvic wall. The preoperative diagnosis was fibroid uterus and left ovarian cyst. The left adnexa and a left rudimentary uterine horn were removed. The operative findings were a bicornuate uterus with a small hematometra in the blind rudimentary left horn. The tube and ovary could not be identified as both were involved in a cystic mass containing old blood which was firmly adherent to the left pelvic wall. (Fig. 1.)

The specimen disclosed a small uterine body the cavity of which was continuous only with the left tube and the ovarian endometrial cyst. It had no connection with the main uterine cavity.

SIGNS AND SYMPTOMS

All but the last patient were between 12 and 16 years of age and had never menstruated. The most common complaint was pain; the sites of which in the order of frequency were low-back, abdominal, and suprapubic. Four patients had urinary complaints as dysuria, retention, or incontinence due to urethral and bladder compression from a distended vagina and uterus.

Incontinence results from overflow. Two of the patients had pain and tenderness with muscle spasm in the right lower quadrant. These

patients are not infrequently operated upon for appendicitis. As a rule the patients were afebrile and not acutely ill. Culture of the vaginal blood in several instances was sterile.

Allergic symptoms such as urticaria, pruritus, asthma, and gastrointestinal disturbances (nausea and vomiting) have been reported.

The *signs* are a bulging, cyanotic, imperforate hymen, and a distended vagina upon which may be superimposed a cystic uterus with lateral, tender, sausage-shaped masses. These adnexal masses are usually fixed by adhesions to the lateral pelvic wall or in the cul-de-sac.

The *etiology* of imperforate hymen is still a disputed question. Most authorities favor a congenital origin, while others believe it is acquired.

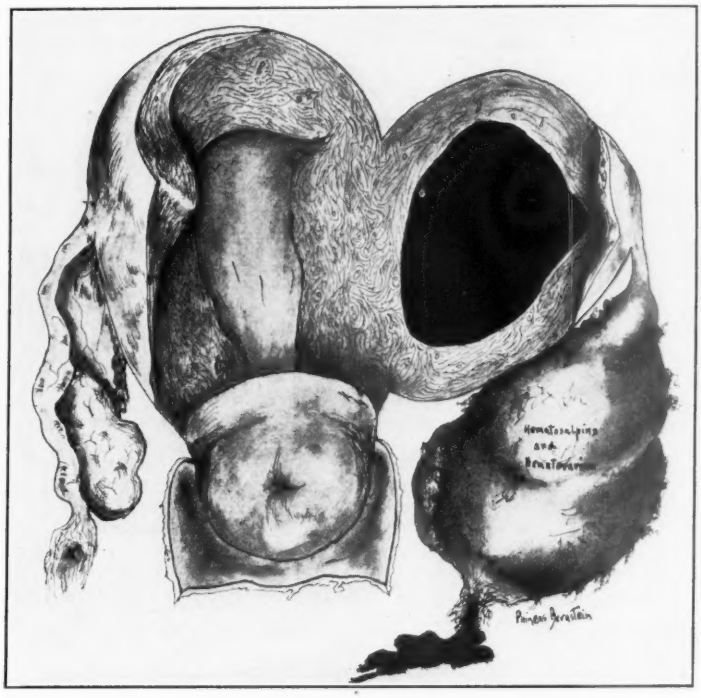

Fig. 1.—Specimen showing blind uterine horn containing hematometra also, hematosalpinx and hematovarium.

In only one of our patients was there a definite history of an acquired cause, namely vaginitis (Case 6). The remaining histories indicate that the origin of imperforate hymen was congenital.

Veit states that a true congenital imperforate hymen produces symptoms in the first six months of life and is due to intrauterine malformation or infection from amniotic fluid. Retained uterine blood, produced by the stimulating action of the maternal female sex hormone on the infantile uterus, causes the hematocolpos and hematometra in the newborn. Moench[16] reported a death in a newborn due to sudden hematometra. Veit also believes that the imperforate hymen producing symptoms at the onset of menses is due to vaginitis acquired

during childhood. Vaginitis may be secondary to an acute febrile illness, such as scarlet or typhoid fever or result from irritating urine or feces. The gonococcus is a well-established offender.

A short statement concerning the development of the female genital tract provides a clearer understanding of congenital malformations. The female reproductive organs are derived from the Müllerian ducts and urogenital sinus. The former are entirely retained; fusion of the lower portions forms the vagina and uterus, while the upper paired free parts give rise to the Fallopian tubes. The lower third of the vagina, however, arises together with the vulva from ectoderm; their point of junction is the most frequent site of malformation (imperforate hymen).

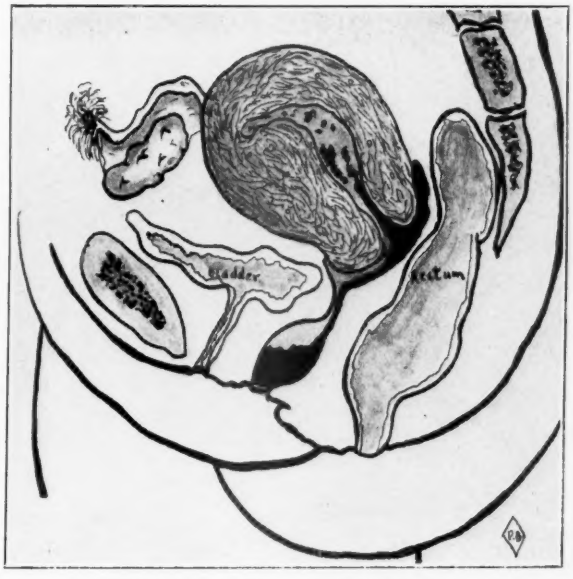

Fig. 2.—Early stage hematocolpos and hematometra due to imperforate hymen.

The pathogenesis of hematometra is completely illustrated by an imperforate hymen obstruction (Fig. 2). At first the vagina becomes moderately dilated by collections of blood and, as maximal distention is produced by further bleeding, the uterus rides above the hematocolpos (Fig. 3). A vulvoperineal prominence appears, the labial folds separate and the bulging, tense, cyanotic, imperforate hymen is exposed. If the latter ruptures spontaneously, the ascending process terminates; if not, the uterine corpus dilates and finally the cervix. Eventually blood, forced into the tubes, escapes into the peritoneal cavity, producing varying degrees of hematosalpinx followed by hematoperitoneum. Pyopneumohematometra and pyopneumohematosalpinx may result if the fimbriated tubal end is closed. The mechanism of closure is identical with that seen in salpingitis (infection) or in ectopic gravidity (aseptic).

Adhesions fixing the distended paper-thin tubes to the pelvic wall add the danger of rupture, hemorrhage, and shock during sudden emptying or manipulation from below. Blood furnishes a fertile culture medium for bacteria which may penetrate the adherent intestinal wall or ascend from below. Rapid and fatal peritonitis may result. Subdiaphragmatic gravitation of blood is common. As much as 3.5 liters of bloody fluid have been removed (R. T. Frank quotes T. Wright[5]).

Hematometra with pelvic endometriosis occurred only twice in our patients. Although these findings support the endometrial displacement theory of Sampson, endometriosis should be a more frequent complication of gynatresia since reflux tubal bleeding is common.

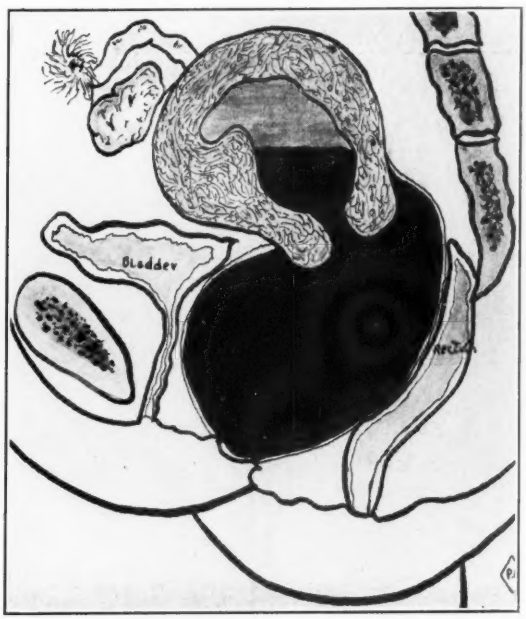

Fig. 3.—Advanced hematocolpos and hematometra due to imperforate hymen.

The end stage of hematometra is characterized by a compression of glandular, vascular, and structural elements (Fig. 4). The inner lining of the entire genital tract is flattened into a single epithelial layer, which permits later regeneration. The entire genital system, by distention, is finally converted into a thin-walled bulbous sac.

The character of the hematometra fluid varies with the patient's age and the site of atresia. During infancy and prepuberty, mucus is conspicuous; in mature patients menstrual elements are the chief constituents, and during the menopause debris and blood (not menstrual) are found. Cervical and vaginal secretions are manifest in all periods but are increased during maturity.

The laked red blood cells are the chief constituents. Lactic acid without the lactic acid bacillus, and mucin, are found. The fluid has a high calcium content but no fibrinogen or fibrin is present. Although

usually sterile the fluid may contain *B. coli* and other organisms which are secondary invaders from blood or lymph streams, from adherent intestine, or are introduced during surgical intervention. The fluid, if infected, is malodorous, purulent, and hemorrhagic, and drains slowly because of its treacle-like consistency. Although the usual amount is 500 to 1,500 c.c., as much as 3,500 c.c.[15] have been evacuated. The color varies from bright red to black. Fluid obtained from 5 cases of hematometra has been assayed for female sex hormone. An estrogenic reaction was present in only one (personal communication from R. T. Frank).

Fig. 4.—Late stage showing hematocolpos, hematometra, and hematosalpinx due to imperforate hymen.

ACQUIRED STENOSIS CAUSING HEMATOMETRA

A. *Cervical Stenosis Due to Cauterization.*—

CASE 12.—This 43-year-old patient, gravida x, para vi, had 4 induced abortions. Her chief complaints were amenorrhea, abdominal pain, urinary urgency, and frequency. The cervix was cauterized one year prior to admission. Pelvic examination disclosed a stenosed cervix which did not permit the passage of a fine probe; a slightly enlarged uterus; and bilateral tender, cystic adnexal masses. At operation, the uterus was found to be enlarged to the size of an eight weeks' gravidity by old blood, and there were also bilateral ovarian cysts and hematosalpinges. A supravaginal hysterectomy and bilateral salpingo-oophorectomy were performed with drainage through the cervix. The pathologic report was "cervical stenosis, chronic hematometra, bilateral hemorrhagic endometrial cysts of the ovaries, and adenomyosis of the uterus." The patient, febrile for ten days postoperatively, was discharged on the eighteenth day.

B. *Instrumental Delivery and Post-Partum Infection, Causing Cervical Stenosis.*—

CASE 13.—This 42-year-old patient, ten months prior to admission, had an instrumental delivery of a full-term stillbirth followed by a mild post-partum infection. Regularly since then her periods were two days to two weeks in duration. A lacerated clean cervix and a normal-sized uterus were found. Partial obstruction of the cervix was encountered at operation and following complete dilatation a moderate amount of old blood escaped. The diagnosis was partial cervical stenosis and hematometra.

C. *Repair of Post-Partum Vesicovaginal Fistula, Causing Cervical Stenosis.*—

CASE 14.—This patient was a 25-year-old gravida ii, para i. Her chief complaint was periodic attacks of suprapubic and low back pain of one and one-half years' duration. Nine years before admission she was delivered of a full-term macerated fetus and sustained a vesicovaginal fistula and third-degree perineal tear. These were repaired one year after the injury. Patient had amenorrhea following delivery which persisted until three days prior to admission when slight bleeding occurred. Pelvic examination revealed a stenosis of the cervix and a soft, cystic uterus enlarged to the size of a three and one-half months' gravidity. At operation the uterus contained 120 c.c. of old blood. There was a right hematosalpinx and a cystic right ovary. The uterus was adherent to the cul-de-sac posteriorly and the bladder anteriorly. A supravaginal hysterectomy and a right salpingo-oophorectomy were performed. Culture of the retained uterine blood was sterile. The postoperative course was uneventful and the patient was discharged fourteen days after operation. Final diagnosis was hematometra and right hematosalpinx secondary to cervical stenosis.

D. *Hematocolpos Secondary to Post-Partum Vaginal Atresia.*—

CASE 15.—This patient, a 22-year-old gravida i, para i, was delivered instrumentally of a stillborn full-term fetus three months prior to admission. Following this she had amenorrhea and continuous urinary incontinence. Pelvic examination disclosed a short vagina with obliteration of the fornices by adhesions. Neither cervix nor uterus could be identified. There was a 3 cm. opening in the anterior vaginal wall which communicated with the bladder. Preparatory to the repair of the vesicovaginal fistula, an attempt was made to release the adhesions in the upper part of the vagina and during this procedure a blind cavity was entered and 8 or 9 drams of old blood escaped.

E. *Cervical Stenosis Following Removal of Cervical Fibroadenoma and Dilatation and Curettage.*—

CASE 16.—This patient was a 43-year-old gravida and para ii who complained of severe abdominal pain, radiating to the back and thighs. She had had a posterior colporrhaphy, appendectomy, ligation of tubes and ventral fixation, followed two years later by a dilatation and curettage for a fibroadenoma of the cervix. Pelvic examination disclosed a completely stenosed cervix and a tense cystic uterus the size of a three months' gravidity. At operation the uterus contained old blood but both tubes and ovaries were normal. A supravaginal hysterectomy and bilateral salpingo-oophorectomy were performed. The postoperative course was uneventful.

F. *Cervical and Vaginal Stenosis Following X-ray and Radium Therapy for Carcinoma of the Cervix.*—

CASE 17.—This 65-year-old woman complained of a painless enlarging, pelvic mass. Her menopause began fifteen years before. Following the diagnosis of carcinoma of the cervix she received x-ray and radium therapy; the exact dosage was not mentioned. Pelvic examination revealed a large cystic, symmetrical mass rising out of the pelvis to four fingerbreadths above the umbilicus. The vagina was completely obstructed by adhesions. At operation a panhysterectomy was performed and a huge distended uterus which contained 800 c.c. of blood was removed. Microscopic study of the uterus showed atrophic mucosa with transitional and squamous cell metaplasia. The postoperative course was uneventful.

G. *Menopausal Cervical Stenosis and Adenomyosis Uteri.*—

CASE 18.—This 51-year-old gravida and para iv had meno-metrorrhagia and lower abdominal pain on the first day of the period, for two years. Her last

menstrual period occurred two months prior. On admission she complained of severe generalized abdominal pains which within twelve hours had localized in the right lower quadrant. There was also moderate uterine bleeding. Physical examination disclosed an acutely ill patient in moderate shock. The blood pressure was 84/54. There was marked bilateral adnexal tenderness. The pelvic organs could not be definitely outlined because of the spasm. Exploratory laparotomy revealed a small amount of blood in the pelvis and under both leaves of the diaphragm. The uterus was soft, cystic and distended to the size of a three months' gravidity. Bilateral hematosalpinges were present. A panhysterectomy was performed. The pathologic report was partial stenosis of the cervix at the internal os; adenomyosis of the uterus; hematometra; bilateral hematosalpinx and hematoperitoneum. The postoperative course was uneventful (Fig. 5).

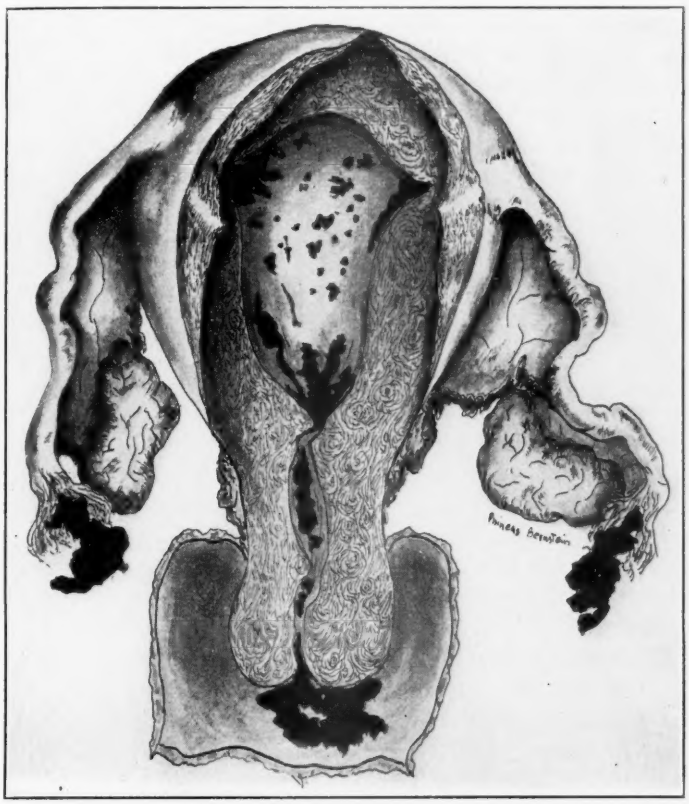

Fig. 5.—Partial cervical stenosis and endometriosis causing partial hematometra, hematosalpinx, and hematoperitoneum.

H. *Cervical Obstruction Secondary to Uterine Fibroids.*—

CASE 19.—This patient was 78 years of age. The climacteric had occurred at the age of 40. Her chief complaint was metrorrhagia of five weeks' duration. In addition she mentioned a large pelvic mass the size of which was constant for the past thirty years. Pelvic examination disclosed a senile atrophic vagina and an irregularly enlarged firm uterus reaching one fingerbreadth above the umbilicus. The sedimentation time was accelerated to fifteen minutes. Dilatation and curettage disclosed a huge distended uterine cavity; but the curettings *showed grossly no evidence of carcinoma.* When the pelvis was explored, a large distended fibroid uterus containing old clotted blood was found. The opened cavity revealed a large, oozing,

adenocarcinoma on the lateral uterine wall. The operation consisted of a supravaginal hysterectomy and a bilateral salpingo-oophorectomy. A small fibroadenoma of the cervix protruded into the cervical canal, causing partial obstruction.

The most common cause of stenosis in this group of cases was injury sustained during delivery, followed by infection (Cases 13, 14, and 15). Cervical stenosis secondary to cervical fibroadenoma was encountered twice (Cases 16 and 19). The other etiologic factors were cauterization of the cervix, x-ray therapy, and involutional cervical changes. Caustics, hyperpyrexia, stem pessaries, gonorrheal and diabetic vaginitis have also been reported.

The syndrome in the female at puberty is generally similar to that in older women, except that in later life the history indicates an acquired cause for the condition. Since at first the acquired stenosis is usually partial, the pelvic organs do not show marked enlargement. A prolonged, diminished, black, tarry flow and occasionally metrorrhagia characterize the menses, and as the block becomes complete, amenorrhea and painful genital tract distention set in. Occasionally dyspareunia occurs.

Acquired hematometra is usually unrecognized until ushered in by general malaise, chills and high fever due to presence of infection. As a rule, however, the general health is not affected and constitutional changes arise only with hemorrhage and infection. A correct preoperative diagnosis in this type of patient is rarely made.

In uncomplicated cases of hematometra and hematocolpos the temperature, pulse, and respiration, as well as blood count and sedimentation time, are within normal limits. When the pain localizes in the right lower quadrant, appendicitis is usually first considered. Congenital anomalies always complicate the picture. A double uterus is confusing, since one uterus may bleed normally or may be enlarged by a fetus, while the other, due to atresia, may contain a hematometra. Pregnancy is simulated by the moderately enlarged, soft uterus, and amenorrhea, and abortion by the intermittent uterine bleeding.

Ectopic pregnancy is suspected in cases of unilateral ruptured hematosalpinx. The amenorrhea, and sudden pelvic pain radiating to the shoulder or subdiaphragmatic region in a patient with an adnexal mass, a soft uterus, rapid pulse (and shock) are identical with the clinical picture of a ruptured ectopic pregnancy.

The treatment of gynatresia is always surgical. The extent and method of the surgical procedure depend on the site and type of atresia, the patient's age, the necessity for preserving the childbearing function, and the presence or absence of infection. The prevention of secondary infection and the establishment of free but slow drainage are the fundamental principles involved. Simple procedures were usually adequate in the younger patients of this group.

Conservatism was employed, particularly in children, since risks of laparotomy and the undesirable effects of castration and sterilization contraindicate radical surgery except as a lifesaving measure. In older women, especially at the climacterium, radical measures were

more reasonably utilized, since benign and malignant tumors often found complicating the hematometra necessitated panhysterectomy; infection, often present, required adequate drainage.

For imperforate hymen, we found complete excision most satisfactory, since there was little danger from sepsis or recurrence. The free double margins of the excised hymen are sutured with interrupted chromic catgut. Patients are kept in bed postoperatively for ten to fourteen days, preferably in Fowler's position to further drainage.

Promoting uterine involution by vaginal tampon, trocar, irrigation, aspiration, and emmenagogues is to be condemned. Pelvic examinations after operation were not performed. Crucial incision of the hymen has fallen into disrepute, since it is followed by recurrence.

Obstructing vaginal septa and membranes are completely excised. Hematometra with vaginal atresia requires a hysterectomy. If construction of an artificial vagina is necessary it may be undertaken later. The skin tube-flap operation devised by Frank and Geist[6] has been used successfully.

For cervical atresias careful dilatation or anterior lip incision are indicated: a rubber tube is inserted into the uterine cavity for drainage. The cervix should be manipulated carefully to avoid rupture of an unrecognized hematosalpinx.

Unilateral hematometra and hematosalpinx in a bicornuate uterus were treated by amputation of the affected side.

Generally the surgeon is guided by the exigencies of the situation when complicated pelvic anomalies are found.

Hematosalpinx is serious due to a potential, if not already present, infection, and most authorities advise an exploratory operation. Since the atresia must also be removed, the problem arises as to which procedure should be done first, the vaginal or abdominal. The advantages of doing the vaginal operation first are: (1) The true pelvic status is more easily and accurately determined after evacuation of vaginal and uterine blood, and (2) if supravaginal hysterectomy is necessary later, abdominal spill of infected blood from vagina and uterus is avoided (Graves).

On the other hand "if the hematosalpinx has already developed, drainage from below will be a real danger on account of an ascending infection" (Reinert). Also bimanual examination following the evacuation of blood from the vagina and uterus may light up a dormant infection or introduce it to the adnexa from below.

Since drainage from below is most often effective in our experience, it is always indicated first in the absence of clinically infected hematosalpinges. However, the patient should be carefully observed for complications. Thus, a laparotomy and the certain loss of part, if not all, of the pelvic organs is avoided. We believe that vaginal examinations are to be avoided whenever possible.

If serious complications have already occurred, such as hemorrhage, peritonitis or tuboovarian abscess, intervention by laparotomy is necessary. Drainage is advisable in these cases because of the accompanying infection.

SUMMARY

1. Nineteen cases of hematocolpos and hematometra are discussed. Eleven were due to congenital anomalies and 9 were secondary to acquired gynatresia.

2. Imperforate hymen is the most frequent congenital anomaly producing hematometra.

3. The etiologic factors causing acquired atresias are childbirth injuries and post-partum infection. Cervical cauterization, x-ray therapy, atrophic changes, and cervical tumors also cause stenosis leading to hematometra.

4. In children, the diagnostic triad is an imperforate bulging hymen, a pelvic tumor and delayed menses.

5. In adults, diagnosis is not as simple, since the gynatresia is usually acquired and partial. Large hematometra are therefore rare.

6. Treatment is always surgical. Conservatism is advocated.

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Ketteringham, Rose C., and Austin, Bruce R.: Blood Sugar During Labor, at Delivery and Postpartum, With Observations on Newborns, Am. J. M. Sc. **195**: 328, 1938.

The mean maternal blood sugar at delivery in 50 cases was 124.6, with 60 per cent of the cases falling between 110 and 140 mg. per 100 c.c., approximately 40 to 50 mg. above the normal range. The mean blood sugar for 47 infants at birth was 103.6; 94 per cent of these infants presented values lower than those of their respective mothers. Both anesthesia and labor have been shown to contribute to the rise in blood sugar at delivery, but there is no indication that the duration of these factors is the primary cause of the rise. The blood sugar of the infant is dependent upon that of its mother, and factors affecting the blood sugar of the mother affect that of the infant. It would seem that the newer obstetric techniques produce no deleterious effects on the glucose metabolism. In 28 cases, comparison showed the blood sugar higher at delivery than during the first stage by a difference in mean of 28 mg. per 100 c.c. The blood sugar of any particular individual two or three days post partum is somewhat higher than normal. The authors established the normal blood sugar range for newborns by the modified Folin-Malmros technique. The first two days of life the blood sugar is 55 to 85 mg. per 100 c.c., with slightly higher values on the third day. Within three to six hours after birth the blood sugar drops to the normal infant range.

J. Thornwell Witherspoon.

A REVIEW OF CESAREAN SECTIONS

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OUR object in presenting this paper is to add 380 cases done during the last five years (1932 to 1937) to our previously reported series of 733 cases; thus giving us a large series (1,113 sections) for study and analysis. This study gives us an opportunity to compare the results of the past five years with those reported in our previous communication: as to incidence, morbidity, mortality, and comparative results for classical and low flap sections. The latter operation was done only rarely prior to 1932 but since then has been performed quite frequently.

1. INCIDENCE

During the five-year period, 1932 to 1937, 11,210 women were delivered at our hospital. Of these, 380 or 3.3 per cent, had a cesarean section. Table I gives the number of deliveries, the number of sections, and the deaths following section for each year of the five-year period.

TABLE I

YEAR	NO. OF DELIVERIES	CESAREAN SECTIONS	DEATHS FOLLOWING SECTION
1932	2,416	72	0
1933	2,259	72	1
1934	2,350	92	0
1935	1,947	74	4
1936	2,238	70	3
Total	11,210	380	8

We further divided this series of cases into two groups: private and general service. There were 7,932 private cases with 297 sections; an incidence of 3.7 per cent or 1 in 27 cases. The number of general service cases was 3,278 with only 83 sections; an incidence of 2.5 per cent or 1 in 40 cases. These facts are shown in Table II.

TABLE II

	NO. OF CASES	SECTIONS	INCIDENCE
Private Cases	7,932	297	3.7% or 1 in 27
Ward cases	3,278	83	2.5% or 1 in 40
Total	11,210	380	3.3% or 1 in 30

We feel that the reason for the greater incidence of sections in private cases as compared with the ward service is that most of the repeat sections, and a large percentage of the cases done for advanced cardiac disease and previous plastic operations are from the private service. In

addition, a large number of men handle the private service and some of them are probably less conservative in their private cases than we are in managing ward cases.

Table III is a composite of the series here reported and the series reported a few years ago, showing a comparison of incidence and mortality for different time periods.

TABLE III

YEARS	DELIVERIES	SECTIONS	INCIDENCE	DEATHS
1908-1916	4,116	122	1:33.7 (3.0%)	1 (0.82%)
1916-1924	7,637	237	1:32.2 (3.1%)	12 (5.1%)
1924-1932	17,425	374	1:46.5 (2.2%)	12 (3.2%)
1932-1937	11,210	380	1:30 (3.3%)	8 (2.1%)
Total	40,388	1,113	1:36 (2.7%)	33 (2.9%)

In the 380 sections done during the last five years, the incidence of 3.3 per cent is certainly greater than in any one of the three other periods shown in the previous table. We believe the reason to be that we are today doing many more sections for placenta previa, cardiac disease, and progressive toxemia, than we used to do in the past. This is brought out rather strikingly in Table IV.

TABLE IV

YEARS	NO. OF SECTIONS	FOR TOXEMIA	FOR PLACENTA PREVIA	FOR CARDIAC CONDITIONS
1908-1932	733	37 (5.0%)	19 (2.6%)	18 (2.5%)
1932-1937	380	32 (8.4%)	24 (6.3%)	24 (6.3%)

2. INDICATIONS FOR SECTIONS

Table V gives the indications in the order of their frequency together with the maternal and fetal mortality for each group. The fetal deaths do not include nonviable fetuses. In cases where several factors indicated the necessity for cesarean section, the most important one is classified as the indication.

Disproportion, either with normal or with contracted pelvis, was responsible for 35.7 per cent of the total number of sections. In this group there was a maternal mortality of 1.4 per cent, and no fetal mortality.

Previous cesarean section was the second largest group with 88 cases or 23.1 per cent; the maternal mortality in this group was 1.1 per cent and the fetal mortality 3.3 per cent. While some clinics allow selected cases to go through labor after previous section, at our hospital we prefer to handle these cases by elective section, usually with sterilization if the woman has one or more living children.

Progressive toxemia, placenta previa, cardiac disease with a history of broken compensation, and previous stillbirths, account for 26 per cent of the cases. During the past five years the percentage of cases handled by section for these four indications has been greater than at any other time in the history of the hospital.

TABLE V

INDICATION	NO. OF CASES	MATERNAL DEATHS	FETAL DEATHS
A. Disproportion	*136* (35.7%)	*2* (1.4%)	*0*
a. With contracted pelvis	96	2	0
b. With normal pelvis	40	0	0
B. Previous cesarean section	*88* (23.1%)	*1* (1.1%)	*3* (3.3%)
C. Toxemias	*32* (8.4%)	*0*	*4* (25.0%)
a. Eclampsia and pre-eclampsia	23	0	3
b. Chronic nephritis	8	0	1
c. Marked essential hypertension	1	0	0
D. Placenta previa	*24* (6.3%)	*1* (4.1%)	*2* (8.3%)
E. Cardiac disease	*24* (6.3%)	*1* (4.1%)	*0*
F. Previous stillbirths	*19* (5.0%)	*0*	*0*
G. Soft part dystocia (operative)	*14* (3.6%)	*1* (7.2%)	*0*
a. Previous myomectomy	8	1	0
b. Vaginal plastics	6	0	0
H. Malposition	*10* (2.6%)	*0*	*0*
a. Breech	7	0	0
b. Transverse	3	0	0
I. Uterine inertia and cervical dystocia	*10* (2.6%)	*0*	*0*
J. Soft part dystocia (nonoperative)	*6* (1.5%)	*0*	*0*
a. Fibroids	4	0	0
b. Double uterus	2	0	0
K. Old primipara with long history of sterility	*6* (1.5%)	*1* (16.6%)	*0*
L. Diabetes	*4* (1.0%)	*0*	*0*
M. Ruptured uterus	*2* (0.5%)	*0*	*2* (100.0%)
N. Ablatio placentae	*2* (0.5%)	*0*	*1* (50.0%)
O. Contraction ring	*1* (0.2%)	*1* (100.0%)	*1* (100.0%)
P. Fractured pelvis	*1* (0.2%)	*0*	*0*
Q. Ectopic kidney in pelvis	*1* (0.2%)	*0*	*0*
Total	380	8	13

The remaining 15 per cent of the sections were done for a great variety of indications as shown in Table V.

3. MORBIDITY

Any patient who had a temperature over 100.0° F. by mouth for more than 72 hours postoperatively was considered morbid. Of the 372 patients who lived, 173 or 46.5 per cent were morbid. This is practically the same as the morbidity of 46.8 per cent reported for our previous series of 733 sections. There is always a marked discrepancy between the classification of morbidity in terms of temperature alone, and morbidity in terms of actual pathology. A good many patients run an elevated temperature for four or five days and yet no definite cause can be found to account for it. Other cases may have a wound infection or a severe postpartum hemorrhage or a low grade endometritis with foul lochia and yet have a perfectly normal temperature. Table VI gives the causes of morbidity in terms of actual pathology.

A good many of the cases in Table VI overlap; e.g., the patient who has a generalized pelvic infection may also have an upper respiratory infection and a wound infection; and such a patient would be charted in all three categories. Thus, the number of patients whose morbidity is explainable in terms of actual pathology, is really quite small when

TABLE VI. CAUSES OF MORBIDITY (IN TERMS OF PATHOLOGY)

Wound infections	53 cases
Endometritis	31 cases
Upper respiratory infection	10 cases
Phlebitis	10 cases
Sepsis	6 cases
Generalized pelvic infection	6 cases
Parametritis alone	5 cases
Pyelitis	7 cases
Postpartum hemorrhage	4 cases
Acute cholecystitis	1 case
Cystitis	1 case
Pulmonary collapse	1 case
Pulmonary infarct	2 cases
Degeneration of fibroid	2 cases
Vesicovaginal fistula	1 case
Omental abscess	1 case
Bilateral parotitis	1 case

compared with the total number morbid in terms of temperature alone. The relationship between morbidity and type of anesthesia will be discussed later. Associated procedures such as sterilization, myomectomy, occasional hysterectomy, and repair of abdominal hernia, seem to have little or no effect on morbidity.

Table VII shows the relation of duration of ruptured membranes, length of labor, and number of vaginal examinations, to average morbidity (number of days of elevated temperature).

TABLE VII

MEMBRANES		HOURS IN LABOR		VAGINALS	
CONDITION	AVERAGE MORBIDITY	NO. OF HOURS	AVERAGE MORBIDITY	NO. OF VAGINALS	AVERAGE MORBIDITY
Intact	3.5 days	0-12	3.6 days	None	3.8 days
Ruptured 1 to 12 hr.	5.2 days				
Ruptured 12 to 24 hr.	5.0 days	12-48	7.1 days	1 or 2	8.7 days
Ruptured 24 to 48 hr.	7.2 days				
Ruptured 48 hr. and over	15.6 days	Over 48	8.3 days	3 or more (only 2 cases)	6.5 days

Table VII corroborates the well known fact that the longer the membranes are ruptured and the longer the patient is in labor before section is done, the greater the morbidity.

4. MATERNAL MORTALITY

In the series of 380 sections, eight mothers died, giving a maternal mortality of 2.1 per cent. This is lower than the previous mortality rate of 3.4 per cent reported by us in our series of 733 cases.

CASE 1.—(1933.) A primipara with double mitral disease and a history of broken compensation before and during pregnancy. Membranes ruptured eight hours; mild pains for seven hours. Classical section with sterilization under local anesthesia supplemented by gas-oxygen inhalation anesthesia. Eviscerated on sixth day postoperative. Wound resutured. Died of general peritonitis on twentieth day after section.

CASE 2.—(1935.) A gravida iv, para iii, with membranes ruptured forty-one hours; in labor thirty-seven hours; three vaginal examinations. Vaginal delivery attempted by forceps after bilateral cervical incisions. This failed. A tentative diagnosis of ruptured uterus was made. Two hours later a Porro section was done under local infiltration anesthesia. Uterus found unruptured; marked retraction ring present. Died of peritonitis on sixth day.

CASE 3.—(1935.) A 35-year-old primipara with a history of sterility of fifteen years; membranes ruptured seven hours; no pains; one vaginal examination. A low flap section done under gas-oxygen-ether inhalation anesthesia. Died of a virulent peritonitis in forty-eight hours.

CASE 4.—(1935.) A 32-year-old primipara with a generally contracted pelvis. Membranes intact; no vaginal examinations; mild pains for fifteen hours. Low flap section under spinal anesthesia. Died of peritonitis on sixth day.

CASE 5.—(1935.) A 31-year-old primipara who had had a deep myomectomy in 1930. Elective low flap section under general anesthesia. Marked bleeding during operation. Patient rapidly went into deep shock and died six and one-half hours after operation in spite of shock treatment and transfusion. Fifteen minutes before death, patient expelled about 800 c.c. of blood vaginally, indicating that there had probably been marked uterine atony with intrauterine hemorrhage.

CASE 6.—(1936.) A 29-year-old gravida ii with a generally contracted pelvis. Membranes intact; no vaginal examinations; mild pains for five hours. Classical section under gas-oxygen-ether anesthesia. Eviscerated on sixth day. Wound resutured; plastic peritonitis found. Died on sixth day, a few hours after resuturing of wound.

CASE 7.—(1936.) A 34-year-old gravida ii with history of previous section. Membranes ruptured thirteen hours; no vaginal examinations; no pains. Low flap section and sterilization under gas-oxygen-ether anesthesia. Died on fifth day of symptoms suggesting pulmonary embolus.

CASE 8.—(1936.) A 30-year-old primipara with a partial placenta previa. Classical section under gas-oxygen-ether anesthesia. Had a small pulmonary embolus on twelfth day postoperative, resulting in a pulmonary infection. Discharged from hospital on twenty-second day while still running a low grade temperature of 100.0° F. Died suddenly after three days at home. Death probably due to a large pulmonary embolus.

TABLE VIII. MATERNAL MORTALITY

CAUSE OF DEATH	NO. OF CASES	INDICATION FOR SECTION	
Peritonitis	5	Contracted pelvis	2
		Cardiac disease	1
		Contraction ring	1
		Old primipara	1
Pulmonary embolus	2	Placenta previa	1
		Previous section	1
Shock—probably due to uterine hemorrhage	1	Previous deep myomectomy	1

Infection and embolus are responsible for 87.5 per cent of the deaths. In our previous series they accounted for 84 per cent of the deaths.

A study of the condition of the membranes, duration of labor, and number of vaginal examinations in the 8 patients who died, fails to reveal any definite relationship between these factors and the death of the patient. The same was true for the 25 deaths in our previous series of sections. However, it is quite likely that in a very large series of deaths following section, some definite relationship could probably be established.

5. FETAL MORTALITY

The gross or total fetal mortality was 21 or 5.5 per cent. Correcting for nonviability, the fetal mortality is reduced to 3.4 per cent.

TABLE IX. FETAL MORTALITY

	TOTAL	NONVIABLE FETUSES	CORRECTED
Stillbirths	10	5	5
Neonatal deaths	11	3	8
Total	21 (5.5%)	8	13 (3.4%)

The gross or total mortality includes stillbirths and neonatal deaths. The only correction made is for nonviability (all fetuses less than twenty-eight weeks old were considered nonviable).

Stillbirths.—Of the 10 stillbirths, 5 were nonviable and 5 were full term. Of the viable stillbirths, two mothers were sectioned for ruptured uterus, one for previous section, one for ablatio placentae and one for contraction ring. Of the 5 nonviable stillbirths, one mother was sectioned for essential hypertension with myocarditis, two for chronic nephritis, and one for advanced cardiac disease (twins).

Neonatal Deaths.—There were 11 babies that died in the first two weeks of life. Of these 3 were nonviable. Of the 8 viable ones, five died of prematurity, two died of pulmonary atelectasis, and one of pulmonary atelectasis associated with multiple visceral hemorrhages.

6. ELECTIVE SECTIONS

One hundred twenty-five patients were sectioned before the onset of labor, with membranes intact, and in the vast majority no vaginal examination was done. One mother died (see Case 5 under maternal mortality), giving a mortality of 0.8 per cent. This group of cases does not include cases of eclampsia or placenta previa.

Forty patients were morbid, an incidence of 32.2 per cent. The morbidity for the entire group of 380 cases was 46.2 per cent.

In our previous series of 733 sections there were 152 elective sections with 3 deaths, giving a 1.9 per cent maternal mortality. Adding the two elective groups together we have 277 sections with 4 deaths, a 1.4 per cent mortality rate. This group of elective cases gives us our lowest mortality. For the 836 nonelective sections (total of both groups) our maternal mortality was 3.4 per cent.

Of the 125 elective cases done from 1932 to 1937 about 50 per cent were done for previous section, about 25 per cent for progressive toxemia, nephritis, and cardiac disease, 10 per cent for previous stillbirths, and the remainder for such indications as deep myomectomy, complete vaginal plastics, abruptio placentae, multiple fibroids, diabetes, etc.

The gross fetal mortality for these 125 elective sections was 10 or 8 per cent; of the 10 babies 6 were nonviable, giving a corrected fetal mortality of 3.2 per cent which is practically the same as the 3.4 per cent corrected fetal mortality for the entire group.

7. TYPE OF OPERATION

Of the 380 cases for 1932 to 1937, 269 sections were of the classical type with 5 deaths, giving a maternal mortality of 1.8 per cent. One hundred and eleven were low flap sections with 3 deaths, a mortality rate of 2.7 per cent. If we add together the classical and low flap sections for the entire series of 1,113 cases from 1907 to 1937, we get the results as shown in Table X.

TABLE X. COMPARISON OF CLASSICAL AND LOW FLAP SECTIONS

	NUMBER	DEATHS	MORTALITY RATE
Classical sections	945	28	2.96%
Low flap sections	168	5	2.97%

The mortality is practically the same for the low flap and classical sections. It must be remembered, however, that we are comparing series of unequal size (945 against 168), and also the fact that a good many of the low flap cases had longer tests of labor with longer periods of ruptured membranes. We feel that the low flap section, while not infallible, offers a definitely greater margin of safety than the classical route for the case that has had a fairly long test of labor or when the membranes have been ruptured for some time.

Six Porro sections were done in the group of 380 cases. Three were done for multiple fibroids, two for ruptured uterus, and one for contraction ring wrongly diagnosed as ruptured uterus. One mother died, giving a mortality of 16.6 per cent (see Case 2). Three babies were stillborn. Of the 5 mothers that lived, 2 were morbid and 3 nonmorbid.

8. ANESTHESIA

In order to eliminate such factors as duration of labor, length of time membranes have been ruptured, and number of vaginal examinations, only elective cases were studied to determine any possible relationship between type of anesthesia and morbidity.

Table XI shows the percentage of morbidity for each type of anesthetic used.

TABLE XI. RELATION OF TYPE OF ANESTHETIC TO MORBIDITY

	TOTAL	CASES MORBID	PERCENTAGE
General	53	19	35.8%
Spinal	45	14	31.1%
Local	26	7	27.9%

While the percentage of morbid cases is not remarkably lower when done under local infiltration, one gets the definite impression clinically that these cases do much better postoperatively than those done under general or spinal. The patients are more comfortable, they rarely vomit or become distended, they can take fluids by mouth six to eight hours postoperatively, and they usually run a slower pulse than with the other forms of anesthesia.

TABLE XII. COMPOSITE TABLE FOR 1,113 SECTIONS 1907 TO 1937

INCIDENCE			MATERNAL MORTALITY			MORBIDITY			FETAL MORTALITY (CORRECTED)			MORTALITY ELECTIVE SECTIONS			TYPE OF SECTIONS			
															CLASSICAL		LOW FLAP	
															945		168	
DELIVERIES	SECTIONS	PER CENT	SECTIONS	DEATHS	PER CENT	SECTIONS	MORBID	PER CENT	SECTIONS	FETAL DEATHS	PER CENT	ELECTIVE SECTIONS	DEATHS	PER CENT	DEATHS	PER CENT	DEATHS	PER CENT
40,388	1,113	1:36 2.7%	1,113	33	2.95	1,113	505	45.3	1,113	40	3.5	277	4	1.4	28	2.96	5	2.97

As far as spinal anesthesia is concerned, about three years ago we had two near-deaths immediately after the spinal injection of neocaine. Since then we have given up its use entirely on service cases and most of us do our private cases under either general or local infiltration anesthesia. We consider spinal anesthesia dangerous for the pregnant woman, as De Lee has been pointing out. We believe local infiltration to be the safest anesthetic for cesarean section as well as the one that gives the patient the most comfortable postoperative course.

9. SUMMARY OF 380 SECTIONS (1932-1937)

Of 11,210 deliveries, 380 were done by cesarean section, an incidence of 3.3 per cent. There were 8 deaths giving a maternal mortality of 2.1 per cent. The number of cases morbid in terms of temperature was 173 or 46.5 per cent. The fetal mortality after correction for nonviability was 3.4 per cent. There were 125 elective sections with one death, giving a maternal mortality of 0.8 per cent for this group. In the elective cases done under local anesthesia the morbidity was somewhat lower than for the cases done under general or spinal anesthesia.

10. SUMMARY OF 1,113 SECTIONS (1907 to 1937)

During this thirty-year period there were 40,388 deliveries of which 1,113 were cesarean sections; an incidence of 1:36 or 2.7 per cent.

Thirty-three mothers died, giving a maternal mortality of 2.9 per cent. The number of cases morbid in terms of temperature was 505 or 45.3 per cent. The corrected fetal mortality for the entire group was 3.5 per cent.

There were 277 elective sections with 4 deaths giving a mortality of 1.4 per cent for this group.

Of the 1,113 cases, 945 were classical sections with a mortality of 2.96 per cent, while 168 were two flap sections with a mortality of 2.97 per cent.

Table XII brings out all the facts mentioned above.

Shelesnyak, M. C., and Rosen, Samuel: Naso-Genital Relationship, Endocrinology 23: 63, 1938.

The periodicity of the estrus cycles of 209 young adult female rats was observed. The effect of treatment of the nasal mucosa with various agents on the estrus cycles was studied in 185 rats with histories of regularity. Control animals received treatment orally. Stimulation with oleum sinapis appeared to affect the regularity of the cycles, chiefly in the follicular phase. Depression effected with tannic and trichloracetic acids produced prolongation of di-estrual phase in 9 of 20 cases. Anesthetization of nasal mucosa with nupercaine produced pseudopregnant state in 58 of 115 cases. Controls which received buccal treatment were negative. Traumatization of the uteri of 16 nupercaine treated animals with prolonged cycles provoked gross decidual growths in 12 cases.

J. THORNWELL WITHERSPOON.

INSULIN TREATMENT OF DYSMENORRHEA

EDNA WATT SCHRICK, M.D., LINCOLN, NEB.

MALNUTRITION has long been known as a constitutional reason for dysmenorrhea. Altschul[1] in using insulin for its metabolic stimulating effect in malnutrition found in dysmenorrhea patients an absence of painful menses while under treatment with insulin. He believed that the improvement of the dysmenorrhea with insulin was due indirectly to the resultant improvement in nutrition; so he decided to try the direct effect of insulin on a patient without malnutrition during an attack of dysmenorrhea. He noted relief in ten out of twelve cases. I became interested in this new, easy method of treatment and decided to try it on a few cases. My interest was stimulated by Miller's statement that probably all the glands of internal secretion play their part in the female menstrual cycle and bear a distinct relation also to the nervous and emotional constitution of women, also by the well-known, but frequently forgotten, fact that the sex glands of girls and women are stimulated by the use of insulin.[5, 6]

I have followed a small series of ten cases for five to six months, giving Squibb's regular insulin, five units daily before lunch for three to five days before each menstrual period for two to three months. The girls used in this study were unmarried college students; ages 16 to 29 years, whose menstrual periods were regular and normal in all respects except for the association of pain of varying degrees of severity. Eight out of ten patients (or 80 per cent) were subjectively benefited while under treatment, and three have had several menstrual periods free from pain without the use of insulin. Further observations and more case studies are necessary before we can say whether or not this work has any permanent effects. Table I gives a summary of the case studies to date.

Corroborating Altschul's[2] findings, I have succeeded in relieving the cramplike pains of dysmenorrhea with a single injection of Squibb's regular insulin, 5-7 units given during the attack of dysmenorrhea with a supply of carbohydrate to counteract the antidiabetogenic effect of the insulin.

Altschul and others[2] have suggested that insulin may work through its hypoglycemic effect. Efforts to control the antidiabetogenic effect of insulin and a few blood sugar studies would seem to discredit this hypothesis. The opposite view of this theory, that hypoglycemia is a cause for dysmenorrhea and not a cure, has been taken by Tedstrom and Wilson.[4] The nausea, vomiting and faint feelings associated with dysmenorrhea suggested the hypoglycemia theory. Fasting blood sugar studies showed no uniform variation in fasting blood sugar levels at menstruation as compared with the mid-menstrual level. Eighty per

TABLE I. CASE STUDIES

	AGE YR.	MENARCHE YR.	DURATION OF SYMPTOMS YR.	ONSET OF PAIN (RELATION TO FLOW)	NUMBER OF INJECTIONS MONTHS	DURATION OF OBSERVATION MONTHS	SUBJECTIVE RESULTS
L. M.	26	11	15	1st day	3	6	Pain relieved
I. R.	16	12	1	1st day	3	6	Pain relieved
H. S.	19	12	4	1st day	3	6	Pain relieved
R. R.	18	12	5	1 day before flow	2	5	Pain relieved
N. M.	25	13	8	1st day	3	3	Relief
A. S.	30	15	10	7 days before flow	2	5	Relief
O. W.	25	11	9	1st day	3	5	Some relief
M. B.	17	11	7	1st day	3	6	Relief
G. W.	20	13	6-7	1st day	3	6	No relief
S. E.	29	13	10	1st day	3	6	No relief

cent of their dysmenorrhea subjects showed a lower blood sugar during menstruation (below 80 mg. per 100 c.c. of blood). These patients were relieved by high carbohydrate feedings and intravenous glucose immediately, but the fact that carbohydrate feeding and intravenous glucose also helped patients with normal or high blood sugars discredits their hypoglycemia theory.

The physiologic explanation of the success of the high carbohydrate feedings and intravenous glucose therapy in the treatment of dysmenorrhea lies in the fact that such therapy may stimulate the pancreas to secrete more insulin, and the favorable results therefore would be due primarily to insulin. This idea is supported by the fact that increasing blood sugar level of patients who had normal or high blood sugars also gave relief. At present, I believe that insulin therapy in functional dysmenorrhea is successful because of its effect on the ovaries. The study of insulin treatment for dysmenorrhea needs further investigation; however the results so far indicate that it is of value in the treatment of this common complaint.

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DERMOID CYST OF THE OVARY WITH PERFORATION OF THE URINARY BLADDER AND OF THE SIGMOID

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OVARIAN dermoid cysts have been reported frequently as the cause of peculiar symptoms because of their tendency to perforate adjacent viscera. Our patient is remarkable because of *pilimictio* (passage of hair in the urine) and the passage of feces and gas by urethra.

The patient was a 36-year-old, para i, white married female. She entered Duke University Hospital Oct. 12, 1937. Menarche was at age of fifteen and her periods had been normal and regular. Her family history and past history were irrelevant. She had had urinary frequency for "as long as she could remember."

In July, 1932, when about four months pregnant, her first and only pregnancy, the patient had an attack of cramplike, lower abdominal pain lasting a day. This was diagnosed as kidney colic. No x-rays were taken and no other diagnostic studies were made. She noticed no hematuria or increase in frequency. Two weeks later she had another attack followed by increased frequency and dysuria. She was treated for cystitis throughout the rest of her pregnancy by oral medication and by bladder irrigations. In December, 1932, following a prolonged labor, the patient was delivered by forceps of a full-term healthy child (10.5 pounds). The puerperium was uncomplicated by fever or hemorrhage but "the left side of the patient's body was paralyzed for three months." The lower extremity was particularly affected. She continued to have dysuria and frequency, and following recovery from her palsy, received two cystoscopic treatments for pyelitis. Except for frequency she was fairly well. In July, 1933 she had a severe attack of lower abdominal pain. The pain lasted for about a day and was followed by great abdominal distention and continuous vomiting. During this episode she was febrile, and her abdomen was so tender that she would not allow herself to be examined. She was in bed about a month. Following this she noticed no change in her urinary symptoms and her bowels moved as usual. She had slight lower abdominal pain and would occasionally have a low grade fever. In July and August, 1935 she had attacks of severe lower abdominal pain lasting about two hours. In February, 1936 she had a severe attack of lower abdominal pain lasting almost six weeks, characterized by remissions of a few days' duration. She again vomited continuously and her abdomen was very much distended. She had considerable fever. With this attack she first noticed the passage of gas and feces through her urethra. This was not continuous and was noted only when her bowels "were loose."

On April 6, 1936 she entered Duke University Hospital for the first time. Physical examination was not remarkable except for the pelvic findings. The external genitalia were normal. The perineum was relaxed and lacerated. The cervix was lacerated and chronically infected. The uterus was twice normal size and firm. Catheterized urine specimens were loaded with pus and had a fecal odor. *B. coli communis* was cultured from the urine. A "flat" plate of the abdomen showed "an elongated area of calcification overlying the left margin of the sacrum, possibly in the soft tissues of the pelvis." A cystogram showed marked compression of the upper margin of the bladder, "probably by an enlarged uterus or fibromyoma." Cystoscopy revealed inflammation around the trigone and normal ureteric orifices. Urine from both ureters showed no pus. The diagnosis of chronic cystitis was made and the patient was given bladder irrigations. She was discharged relieved of bladder symptoms on April 15, 1936.

She continued to have marked dysuria and frequency. When seen in the Out-Patient Department on July 7, 1936, the fundus of the uterus was normal in size and no masses were palpable.

She reentered Duke University Hospital on Aug. 6, 1936. Nothing remarkable had occurred in the interval. The uterus was found to be slightly enlarged and again no adnexal masses were palpable. The bladder wall felt thick and tender. Her urine was again found to be loaded with pus. Cystoscopy revealed slight trigonitis. She was found to have a residual urine of about 30.0 c.c. X-ray films showed the calcified area in the pelvis unchanged. She was discharged on Aug. 11, 1936 with the diagnosis of chronic cystitis and was given a ketogenic diet.

Dysuria, frequency, and occasional passage of feces and gas through urethra persisted. In May, 1937, she had a sudden attack of massive hematuria lasting three weeks. In June, 1937, she first noticed the passage of hair and small calculi by

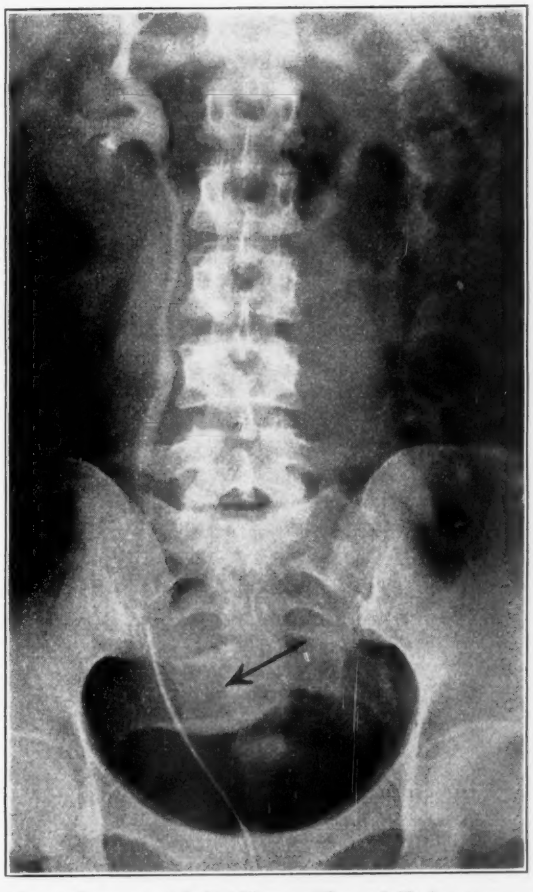

Fig. 1.—Retrograde pyelogram of left kidney. The calcified areas and the deformity of the bladder are visible.

urethra. After the hematuria subsided she was cystoscoped weekly by her local physician. Small masses of hair and stones were removed from her bladder and bladder irrigations were given. In July a tuft of hair was found protruding into the fundus of the bladder and the diagnosis of perforating dermoid cyst was made.

On Oct. 12, 1937 the patient again entered Duke University Hospital. Physical examination showed normal temperature, pulse, respirations, and blood pressure. The only significant findings were slight tenderness and spasm in the left lower quadrant of the abdomen. Pelvic examination showed normal external genitalia, relaxed and lacerated perineum, small cystocele, and small rectocele. The cervix was lacerated and eroded. The fundus was normal size, anterior, and movable. Anterior

and to the left of the uterus an ovoid mass about 4.0 by 8.0 cm. was palpable. The right vault was negative. The diagnosis of dermoid cyst of the left ovary with perforation of the bladder was confirmed. A catheterized specimen of urine was loaded with pus and *Staph. aureus* was cultured. Her hemoglobin was 80 per cent (Sahli), red cell count 4,210,000, and white count 6,960. Differential counts were within normal limits. Sedimentation rate was 10.0 mm. in thirty minutes. Her Kahn and Wassermann tests were negative. Cystoscopy showed a tuft of hair about 6.0 cm. long protruding through a fistula on the left side of the fundus of the bladder. The opening appeared about half a centimeter in diameter. A flat x-ray plate of the abdomen showed the calcified area on the left of the pelvis unchanged. Barium enema showed a small irregularity along the lower margin of the sigmoid

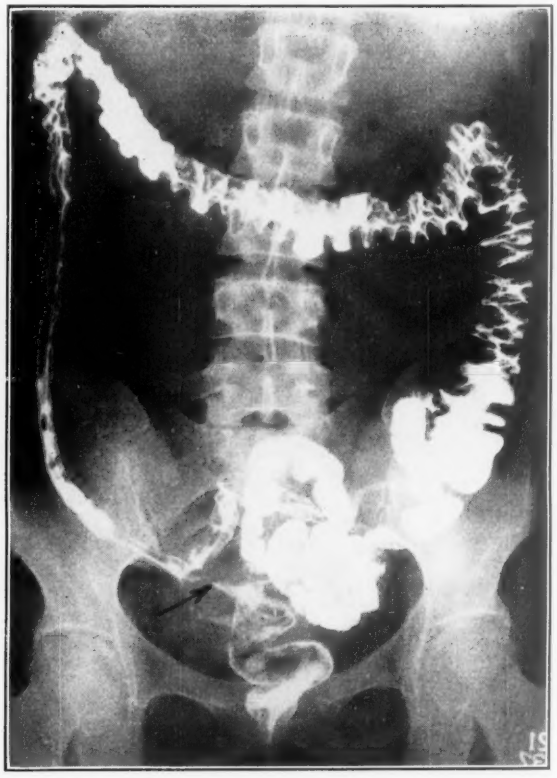

Fig. 2.—Barium enema after expulsion. The fistulous tract extends through the calcified area.

and a narrow collection of barium that extended past the calcified area to the region of the bladder. This was considered to have been caused by a small sinus tract extending from the sigmoid.

On Oct. 20, 1937 celiotomy was performed under gas, oxygen, and ether anesthesia. A midline suprapubic incision was made. A knuckle of sigmoid was adherent to a mass of adhesions on the left side of the pelvis. The uterus was obscured by a fold in the bladder which was adherent across the fundus and to both broad ligaments. The right tube and ovary were grossly normal and were adherent lightly to the posterior surface of the broad ligament. The pelvis was carefully isolated by packing and the sigmoid was dissected free. It was adherent to a cystic structure about 4.0 by 8.0 cm. in diameter which was densely adherent to the left anterior region of the bladder. The left ovary was a small cystic structure about 4.5 cm. in diameter and was connected to the cyst only by a few fibrous strands. The sigmoid com-

municated with the cyst through a fistula about 0.5 cm. in diameter. The defect in the sigmoid was closed with a double layer of inverting sutures. The bladder was then freed, and the dermoid cyst excised from its attachment to the bladder. The fistulous tract communicated through the dermoid and a tuft of hair about 6.0 cm. long, lightly encrusted with calcareous material, was pulled out of the bladder as the cyst was removed. The opening in the bladder was slightly enlarged and infolded with a double layer of continuous sutures. The remnant of the left ovary was excised and the abdomen drained by posterior colpotomy.

An inlying catheter was left in the bladder for nine days, and she was given 0.25 per cent acetic acid bladder irrigations every two hours. A rectal tube was left in place most of the time for the first five days, since no cecostomy had been performed. For three days postoperatively the patient was given nothing by mouth

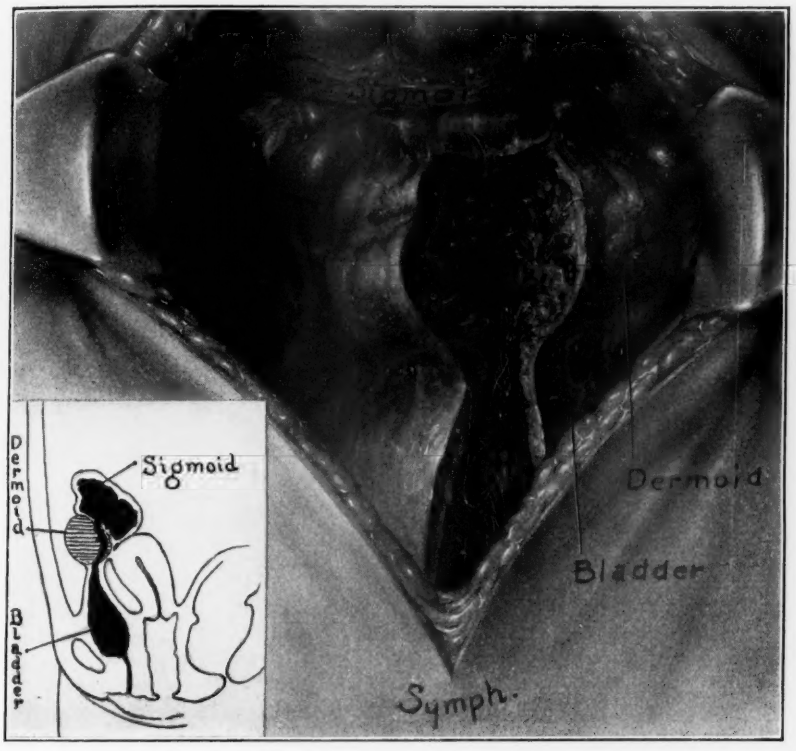

Fig. 3.—Diagram of the findings at operation.

and received parenteral fluids. Her temperature and pulse dropped to normal and she was given liquids by mouth. She passed much flatus by rectal tube. The abdominal wound healed by first intention. Vaginal drains were removed on the seventh day. This was followed by the drainage of considerable amounts of foul pus from the vagina. On the eighth postoperative day the patient developed a small perianal abscess. It was incised under gas-oxygen anesthesia on the tenth postoperative day. Her bowels thereafter moved spontaneously with mineral oil. She was discharged on the eighteenth postoperative day completely relieved of her symptoms.

The pathologic report was as follows: "The specimens were a large dermoid cyst and a smaller cystic structure. The dermoid was 2.0 by 4.0 by 8.0 cm. and was bilocular. Between the lobes was a groove containing hair and feces. On section the locules contained clear fluid and there was much calcium in their walls. There were some papillomatous outgrowths in the lining. The smaller cyst was 4.5 cm. in diameter, unilocular and had a smooth lining. Microscopically there was no evidence

of malignancy in the dermoid. Stratified epithelium and numerous glandular structures were present. There were some brain tissue, much bone and cartilage and one area that showed a collection of renal tubules. The smaller structure proved to be a simple cyst with a fibrous wall and an endothelial lining.''

The patient returned to the dispensary three months after the operation. She was completely relieved and had gained weight. Cystoscopy revealed a small reddened plaque at the site of the urinary fistula. Her urine was entirely normal.

The above patient is interesting because of the accuracy with which her symptoms can be interpreted in retrospect. The dermoid obviously had its origin in the left ovary. During her pregnancy in July, 1932 the initial attack of pain was probably due to torsion of the pedicle. The ''paralysis'' post partum was apparently due to some cause totally unrelated to her pelvis, as the size and the anterior position of the cyst would have prevented any pressure on the lumbosacral plexus. The at-

Fig. 4.—Posterior view of the dermoid after removal.

tack of fever, distention, vomiting, and abdominal pain in July, 1933 was undoubtedly due to peritoneal irritation. At that time the dermoid was probably completely separate from the ovary. The attack was caused either by infection in the cyst or leakage of some of the contents with the production of a sterile peritonitis. Feces and gas appeared in the urine in February, 1936, and at that time the dermoid was probably receiving its blood supply entirely from the sigmoid and bladder. The mass felt in April, 1936 may have been due to the accumulation of feces in the cyst or to incomplete evacuation of the contents. The mass disappeared in August, 1936 because of escape of the cyst's contents and the collapse of its fibrous walls with the better establishment of the fecal fistula. The mass palpable on her last admission was due to enlargement of the subsidiary locules.

Ewing[22] has stated, ''The dermoid may migrate from the ovary and become implanted elsewhere or perforate the hollow viscera.'' The etiologic factor in the formation of fistulas appears to have been primarily interference with the blood supply of the dermoid and subsequent infection of its contents. In none of the cases reported was malignancy a factor.

Haggard[11] in 1907 reported the case of a woman in which a right-sided dermoid had ulcerated into the cecum and bladder. Derveaux[15] in 1909 reported a patient in whom a dermoid had involved both the rectum and bladder. He marsupialized the cyst and allowed the fistulas to close spontaneously. Thomas and Exley[26] in 1930 reported a patient with a dermoid cyst opening into the bladder, an appendiceal abscess, the ileum and sigmoid. According to Szathmary,[30] Mayeda and Slimgava's patient had a dermoid communicating with a loop of small bowel and the bladder. No other patients in whom both bladder and bowel were involved by perforating dermoids appear to have been reported. More numerous references are available to dermoids that have involved a single viscus, including even the gallbladder, the abdominal wall, peritoneal cavity and vagina.

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The uterine tube shows automatic contractions and actual peristalsis when removed. Such automatic contractions are demonstrable in every portion of the tube. This peristalsis is produced by both the circular and the longitudinal muscle fibers. The peristaltic rhythm varies between 2 and 6 per minute, begins at the ampulla and passes down to the cornual end. The stimuli for these peristaltic contractions arise in the muscle fibers of the tube as well as in the ganglion cells.

There are only minimal contractions during menstruation; they are most pronounced at the time of ovulation.

These isolated tubes respond to temperature, pH concentration, medications, hormones and bacterial products. The optimum temperature is 37.5 to 38° C. Lower temperatures inhibit and increased temperatures increase peristaltic activity. The optimal pH is 7.4. Barium chloride increases peristalsis to the point of tetany. Ethyl alcohol stimulates in small doses and inhibits in large doses. Lipiodol, alkaloids such as nicotine, adrenalin, ergot, pilocarpine and eserine increase peristalsis. Large doses of alkaloids, atropine, papaverine, etc., decrease peristalsis. Estrin and corpus luteum hormones slightly stimulate peristalsis. Prolan has no direct effect but sensitizes the tube to the action of estrin.

RALPH A. REIS.

NEPHRECTOMY FOR UNILATERAL TUBERCULOSIS FOLLOWED BY PYELITIS IN THE REMAINING KIDNEY DURING PREGNANCY*

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NEPHRECTOMY for unilateral tuberculosis followed by a pyelitis in the remaining kidney during pregnancy has not been reported before. Nephrectomy during pregnancy for all types of kidney pathology is uncommon; nephrectomy for tuberculosis during pregnancy is rare. Stevens[1] in 1924 published a collected series of 18 cases including 2 of his own. Since that report 5 cases were reported by Pugh,[2] Ravina[3] reported 3 cases, and Andrè[4] reported 1 case.

The essential symptom complex is not typical. The right kidney is more frequently involved than the left. In the cases reported the disease has been diagnosed from the second to the eighth month of pregnancy. The onset has been insidious in most cases. There has been usually frequency of urination and nocturia. Dysuria has been a variable complaint. Gross pyuria may be present especially if there is a secondary infection; on the other hand the urine is frequently clear with no albumin or only a faint trace showing. Hematuria occurs frequently and early, often pointing the way to the diagnosis. The physical signs were often inconspicuous; the majority of cases were afebrile and had mild to moderate costovertebral tenderness. In some cases there was suprapubic tenderness. Urinalysis was not always helpful. The incidence of positive smears for the tuberculosis bacillus in the urine varied with different investigators from 25 per cent to 100 per cent. Invaluable and often the sole diagnostic aid have been cystoscopy and intravenous urography. Both these procedures have been important in ruling out other kidney nephropathies, such as calculus, pyonephrosis, and tumors.

In evaluating the results of treatment by other investigators, statistics show nephrectomy is the procedure of choice for unilateral *surgical* tuberculosis. In the 18 cases reported up to 1924, 12 patients had nephrectomies and they all recovered. In 5 nonoperated cases 3 had acute exacerbations, 1 died in the eighth month, and in 1 no noticeable change was noted. In the operated group 6 living children were delivered at term; 2 patients aborted, 1 miscarried two months after operation, and 1 delivered a premature dead fetus at seven months, four months after her nephrectomy. The outcome of the pregnancy was not mentioned in 2 cases. In the 5 nonoperated cases 2 patients aborted; 1 infant was infected at birth and died of tuberculous meningitis eight months later; the fourth case delivered a living normal child at term. The result in the fifth case was not mentioned.

Pugh in 1936 reported 5 cases of nephrectomy for unilateral tuberculosis, the largest individual series, with no maternal or fetal mortality. Ravina in 1931 reported 3 cases; in 2 the mother and child recovered. The third patient was operated upon postpartum but died on the eighth day postoperative. Andrè's patient was operated upon in the third month; the patient had a premature labor four months later.

When one considers the comparative results obtained in the operated and nonoperated cases cited above; when one realizes that the mortality for the mother in kidney surgery, quoting Mussey,[5] is no greater than the same type of surgery in nongravid women; then it is our opinion that pregnancy offers no contraindication for nephrectomy in cases of advanced unilateral kidney tuberculosis.

Most authorities agree that future pregnancies should be discouraged, but if the mother is insistent consent should not be given, quoting Matthews,[6] Stevens, and Schmidt,[7] until the patient has been symptom-free for from two to three years.

*Presented to the Section of Obstetrics and Gynecology at the Academy of Medicine, December 28, 1937.

CASE REPORT

The patient was a 26-year-old white multipara, gravida ii, para i who attended our ante-partum clinic on April 7, 1937. The family and past history were negative. Menses never showed any aberrations. The last menstrual period was Nov. 7, 1936. The expected date of labor was Aug. 14, 1937. Her previous pregnancy three years ago was normal; the child is now living and well. The patient was five and one-half months pregnant at the first examination. Except for a systolic murmur heard at the apex with no evidence of decompensation the physical examination was negative. The Wassermann was negative. The blood pressure was 100/60. The weight was 148 pounds. Urine examination was reported negative except for a faint trace of albumin. In the next 4 visits to our clinic there was a faint trace of albumin in the urine reported on 2 occasions and on the 2 other occasions were reported as completely negative. The patient had no complaints during this period and no

Fig. 1.—Intravenous pyelogram showing a seven months pregnancy. Function of the left kidney was normal. The right side showed no function.

abnormal findings were noted until seven weeks after registration when she was admitted to Beth Israel Hospital with the following complaints:

1. **Hematuria.**
2. Pain—dull in character, in the right lumbar region and suprapubically.
3. Frequency and nocturia.

} All of 2 days duration.

Physical examination on admission was essentially negative. Temperature was normal. Blood pressure was 126/80. There was no costovertebral or abdominal tenderness present, no kidney masses were palpable. X-ray of the chest was negative. Laboratory data: R.B.C., 3,000,000; Hg., 68 per cent. Blood chemistry was normal.

The first clue as to the essential pathology was disclosed by cystoscopy. The bladder was normal. The left ureteral orifice, ureter, and kidney were normal. The right ureteral orifice showed a bullous edema, biopsy of this tissue subsequently was reported as inflamed tissue. There was an impassable obstruction to the

ureteral catheter at ½ cm. from the ureteral orifice. When pressure was exerted on the right kidney, there was bleeding and a ribbon of pus resembling tooth paste expressed into the bladder.

Intravenous pyelogram (Fig. 1) revealed a normally functioning left kidney with slight generalized dilatation of the ureter and pelvis of the kidney. There was some blunting of the calyces. The right side showed an irregular shadow, which was also present on the flat plate, and was interpreted as inspissated pus. This shadow did not show up in the reproduction (Fig. 1). Catheterized specimen of urine from the bladder was negative for the tuberculosis bacillus; the specimen from the left kidney cultured *B. coli.* The diagnosis of the genito-urinary consultant was "nonfunctioning pyonephrotic right kidney with stricture of the lower right ureter, quite likely tuberculous in origin."

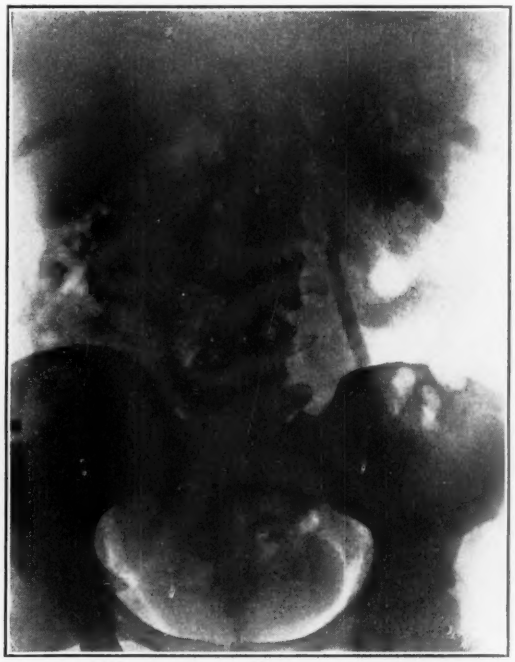

Fig. 2.—Intravenous pyelogram ten days post partum. Left kidney normal except for some enlargement in transverse diameter. Some blunting of the calyces and moderate dilatation of the left ureter. Bladder filled normally.

Consequent preoperative, voided specimens of urine were negative for tuberculosis, except for one specimen which showed an isolated acid-fast bacillus. At the time this one finding, we believed, could not be accepted as positive evidence of the tuberculous origin.

Nine days after admission, under gas-oxygen-ether anesthesia a right nephrectomy was done by Dr. Wilhelm of the genito-urinary service. About 10.5 cm. of the right ureter was removed. The right kidney was greatly enlarged and distended. The cortex was completely atrophic, only a cystic membrane remained. The ureter was thickened and indurated.

The essence of the microscopic report of our pathologist Dr. Plaut was as follows: "There are many tubercle-like formations and giant cells at the inside of the distended calyces. The giant cells for the most part resemble the foreign body type and often are situated in the neighborhood of spaces whose shape is suggestive of fatty acid crystals. The centers of many of the tubercle-like formations contain leucocytes. Extensive search for tuberculosis bacilli was negative."

Provisional Pathologic Diagnosis.—Infected hydronephrosis with foreign body inflammation. No evidence of tuberculosis.

The patient's postoperative course was smooth and uneventful. She was discharged to the prenatal clinic on the fifteenth postoperative day with the wound completely healed except for a small sinus at the site of the drainage tract.

One month later the patient was re-admitted acutely ill with a temperature of 102.6° F. She was suffering with chills and fever, dysuria, frequency, and left lumbar pain for two days. Physical examination revealed left lumbar tenderness with no mass palpable. The uterus was about the size of an eight months' pregnancy. The fetal heart was in the R.L.Q.; the rate was 130 per minute. The position was R.O.A.

Cystoscopy at this time revealed the following: the bladder and the left ureteral orifice were inflamed. The left ureter was catheterized for 14 cm. where an impassable obstruction was met. Following the removal of the catheter a rapid flow of concentrated, blood-tinged urine followed. Indigo-carmine in good concentration appeared in fifteen minutes. Culture of the specimen revealed *B. mucosus capsulatus;* no acid fast organisms were found. The diagnosis was pyelitis. One hour after

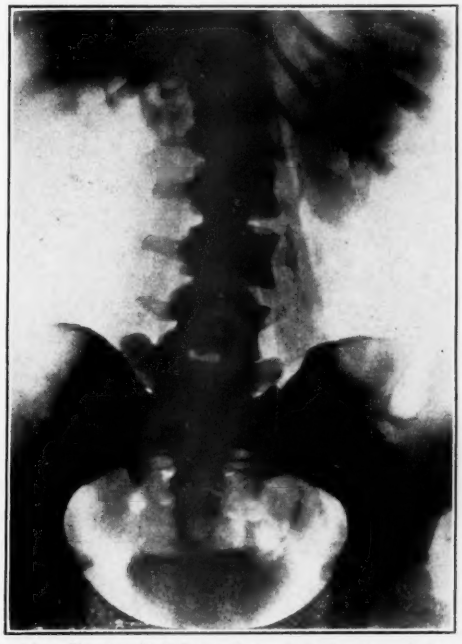

Fig. 3.—Left kidney visualized, slightly enlarged but normal in shape and position. Pelvis, kidney calyces, ureter, and bladder filled well. Function was excellent.

cystoscopy the patient's membranes ruptured spontaneously and she went into labor, delivering in three hours a normal, male infant, weighing 7 pounds 3 ounces. In forty-eight hours the temperature was normal. The urine was clear in nine days on urotropin and acid sodium phosphate. She was discharged after an uneventful postpartum course on the thirteenth day.

Nine weeks later, the patient was re-admitted to the hospital for the treatment of 2 pin-point discharging sinuses at the site of the nephrectomy wound. She had no complaints. At this time a third intravenous pyelographic study was done.

This last plate illustrates strikingly how well the kidney and ureter recovered from the double burden of pregnancy and infection.

Although many urine specimens had been examined during the first and second admissions, only 1 specimen had shown an isolated acid-fast bacillus. During her third admission, five months after the beginning of her illness, a twenty-four-hour specimen of urine revealed positive evidence of the tubercle bacillus.

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THE EFFECT OF IRRADIATION ON THE FUNCTION OF THE OVARY IN YOUNG GIRLS

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NOT infrequently there is a hesitancy to employ irradiation as treatment for gynecologic or other conditions near the ovaries in young women because of the quite general but mistaken belief that such therapy inevitably produces a permanent sterilizing effect. Especially is this the case when irradiation is requested for girls under the age of puberty.

It cannot be denied that there would appear to be some reason for such a supposition. In the early days of x-ray therapy, Halberstaedter[1] was first to note the special sensitiveness of ovarian tissues to these rays, and later Bergonie and Tribondeay[2] enunciated the axiom that the more embryonic the tissue the more sensitive it is to irradiation, so that it was not illogical to expect that the ovaries of young girls would be especially sensitive to irradiation.

Although experience has taught that the younger the woman the more responsive to irradiation when employed in suppressing menstrual function, yet it has been noted likewise that the younger the woman treated, the greater the likelihood of reparation and restoration of function and the less probable permanent sterilization.[3]

As for permanent injury to the ovum contained in the ovary, it is our opinion that the immature graafian follicles, while likely to be affected by irradiation because of their embryonal character, may later recuperate sufficiently to mature, become fertilized and produce normal children. This has occurred in cases where moderate irradiation is employed and in young females where sterilization has been only temporary, so that subsequent menstruations have been followed by normal production of ovum which were capable of fertilization resulted in the development and birth of a normal, healthy baby.[4]

The case herewith presented referred to me by Dr. Pol N. Coryllos, is an example of intensive irradiation administered for pelvic tumor, to a girl 4 years old with both x-ray and radium therapy directed through the pelvis over a long period of time. Treatment was given when the patient was but four years of age and at present she is 14 years old and has been menstruating normally for twenty-one months, menstruation having begun at 12 years of age.

CASE HISTORY

H. P., aged 4 years, was referred for treatment April 5, 1928, for a large tumor of the pelvis situated over the coccyx area, palpable through the abdominal wall and the rectum. The mass almost completely occluded the rectal canal and the small examining finger could not be passed beyond it. The x-ray showed a large dense mass in the pelvis seemingly attached to the coccyx. From May, 1928, until July, 1928, she received high voltage x-ray therapy through the anterior and posterior pelvis, receiving a dose of 1200 r. (measured in air) (in today's measurement). In November, 1928, a radium applicator was inserted in the rectum and a dose of 990 mg. hours given. In January, 1929, the patient was examined and the mass was still unchanged although there was a definite relief of rectal blockage. Further x-ray therapy was advised and during January, 500 r. (measured in air) was given. The patient returned again in April, 1929, and the mass was somewhat smaller. Additional x-ray therapy of 400 r. (measured in air) was given through the pelvis.

Fig. 1.—Patient at four and fourteen years of age.

The patient was seen again in January, 1930. The mass though smaller but still being palpable, 600 r. (measured in air) of x-ray therapy was administered. Until May, 1931, the patient did not report for observation. At that time, she was 7 years old and the mother thought the mass had grown. Examination did not reveal any increase in size of the tumor mass, but because it was still palpable additional x-ray therapy was given, 600 r. (measured in air) being administered.

She was seen again by us on Sept. 11, 1936, her weight was 122 pounds, the mass was slightly palpable, but she had no difficulty with bowel movement. Her menstruation began without difficulty March 27, 1936, when she was 12 years old and has continued in a normal manner since.

The patient was examined on Sept. 9, 1938, by Dr. Coryllos who reports her in excellent condition, no mass being palpable at the site of the former involvement, and the patient had continued to have normal menstrual periods.

CONCLUSIONS

X-ray therapy is not necessarily destructive to ovarian tissues. The younger the patient the less probable is sterilization by irradiation to be

permanent. Normal menstrual periods can occur at puberty and proceed regularly thereafter in young women previously treated by x-ray therapy.

NOTE: A personal communication from Dr. Geo. L. Streeter, Director of the Carnegie Institute Department of Embryology, contains the following suggestion:

"I believe the factor involved in your case is the principle that the more primordial the cells the more resistant they are to x-rays, whereas, ova in the later stages of their differentiation are easily destroyed by x-ray and the primordial cells which will produce their successors are perhaps not so easily affected. In your case the heavy treatment that the patient received certainly killed off all the follicles but in the course of time the primordial ovarian tissue produced a new crop of eggs along with their accessory cells and this finally resulted in the resumption of menstruation."

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55 EAST 86TH STREET

Klaften: Treatment of Pruritus Vulvae and Certain Forms of Dermatitis, Zentralbl. f. Gynäk. **61:** 972, 1937.

During the last three years Klaften treated 38 women with intractable pruritus vulvae with estrogenic hormone. Most of them had previously been treated in various ways, some even with roentgen rays. The youngest patient was 30 and the oldest 82. At first the author administered estrogenic substance hypodermically and by mouth but later resorted to percutaneous inunction of the estrin locally. For the latter procedure, seven times the hypodermic dose is necessary to accomplish the same results. A salve is prepared and a sufficient amount of it rubbed into the skin locally so that 4,000 units are applied daily. As improvement becomes evident, the treatments are given every second day and then with lessened frequency. The patient should be warned that at the beginnnig of the treatment there is often an increase in itching for a while, just as with intramuscular use of estrin. In some cases the author combined hypodermic administration with percutaneous application of estrin. He employs estrin treatment for other dermatatides due to ovarian hypofunction.

The hormone treatment of pruritus vulvae cured 25 of the 38 patients (65.7 per cent) for 6 to 30 months. In 4 cases (10.5 per cent) there were recurrences 9 to 21 months later, but a new course of estrin treatment brought about cure.

In many cases the breasts became enlarged, and in women past the menopause occasionally uterine bleeding was started. The author encountered some women who could not tolerate estrogenic substance; swelling of the extremities, face, hands, vulva and anal regions and a generalized pruritus developed. These symptoms can be avoided by using the estrogenic substance percutaneously.

Excellent results were obtained in women with ovarian hypofunction but not in women with normal ovarian function. The latter had severe reactions following both hypodermic and local applications, and the treatment had to be stopped. Likewise, women with a three-week cycle were not helped by estrogenic substance. The author warns against the use of radiation therapy in women within the menstruating age, especially since this form of treatment does not benefit them. For these patients he advises foreign protein injections.

J. P. GREENHILL.

TREATMENT OF VAGINAL MONILIASIS WITH SILVER PICRATE

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IN RECENT years attention has been directed to infections of the vagina which were formerly thought to be nonspecific. Among these is a vaginal discharge due to *Monilia albicans*, a fungus found on the oral mucous membrane of infants and in the vaginas of pregnant and nonpregnant women. Occasionally severe and acute dermatitis may be produced by the organism; and rarely, where a constitutional disease has resulted, autopsy has demonstrated abscesses in the lung, spleen, kidney, and brain.[1] Sprue, a disease characterized by diarrhea, is also a form of moniliasis. However, most investigators believe that sprue is caused by a distinct species of monilia, *M. psilosis*[2] and *M. enterica* (Castellani).

Monilia albicans appears to occupy an intermediate position between the true molds and the yeasts, producing mycelia and yeastlike forms in both lesions and cultures. The organisms are oval in form, measuring from 5 to 6 microns in length, and about 4 microns in breadth. The mycelia, on the other hand, vary both in thickness and in length, showing many intermediate stages between budding and a typical mycelium.

The problem of identifying and classifying fungi is still a controversial one, and therefore many synonyms are used to describe the organism *(Monilia albicans, Oidium albicans, Saccharomyces albicans)* and the disease produced by it (moniliasis, thrush, sprue).

DIAGNOSIS

Monilia albicans, when present in the vagina, is commonly found in caseous white patches on the vaginal mucosa and cervix. With the patient in the lithotomy position an unlubricated speculum is inserted into the vagina and a smear is taken from the white area with a sterile applicator. The applicator and specimen are placed in a test tube containing 3 or 4 c.c. of normal saline or modified Ringer's solution,[3] and stirred. A drop of the diluted specimen is placed on a slide and examined microscopically, first under the low and then under the high power dry lens. The presence of yeast buds and mycelia constitutes a positive diagnosis. A confirmatory cultural diagnosis is easily obtained by streaking a slant of Sabouraud's agar upon which growth is apparent in twenty-four hours in positive cases. In cases presenting these caseous white patches clinically there is usually a copious white discharge, acetic in odor, which is irritating to the skin as it discharges from the vagina over the external genitalia and the inner aspect of the thighs. A marked

and acute dermatitis of the external genitalia and the femoral regions may result. This dermatitis usually starts when the mycelia invade the skin of the irritated areas and form pustules. These break and spread the infection over a larger area until the final picture presents deeply encrusted regions with an increased number of pustules. Diagnosis may also be made by microscopic examination or culture of material obtained from these pustules.

In the older chronic cases of moniliasis, no discharge or caseous patches are present, but the vagina may present a dry, encrusted appearance.[4] These cases may also be diagnosed by the method described above. Moniliasis differs from trichomoniasis in that the infection, if it does not reach the dermatitis stage, is self-limiting, while trichomonas infections increase in severity unless treated.

TREATMENT

Moniliasis will respond to treatment with many common antiseptics such as 2 per cent aqueous solution of gentian violet. In our study silver picrate was found to be as effective as gentian violet, without the disadvantage of the intense staining. After a positive diagnosis has been made, the vagina is cleansed with a cotton sponge saturated with a suspension of kaolin in aluminum hydroxide.* The vagina is then rinsed with sterile water and dried. This procedure removes the debris and mucus present in the vagina and on the cervix which might protect the tissue from the medicament.

If a plug of mucus is present in the cervical canal or external os, it must be removed because it may serve as a site for reinfection. The removal of this mucus sometimes causes slight vaginal or cervical bleeding, due to the removal of the mycelia from the vaginal mucosa and the cervical glands and tissue.

The next step in the treatment is to paint the vagina with a 1 per cent aqueous solution of silver picrate. Then 5 gm. of 1 per cent silver picrate in kaolin are insufflated into the vagina by means of a vaginal powder insufflator. This constitutes the initial treatment, which is repeated at weekly intervals, or oftener, as required. In the more severe cases in which the vagina was dry, powder insufflation was not used since this further drying proved more irritating. The treatment of such cases is limited to painting the vaginal tract with a 1 per cent aqueous solution of silver picrate.

RESULTS

As shown in the table, 19 cases (Cases 1, 3, 5, 6, 7, 8, 10, 11, 13, 15, 16, 17, 19, 20, 21, 24, 25, 27, and 28) were found positive by smear and culture for monilia. All had a vaginal discharge. They were negative for *Trichomonas vaginalis* and no dermatitis was present. Two cases (Cases 12 and 18) doubtful on smear, proved to be positive on culture, neither one presenting a dermatitis. One case (Case 18), however, showed *Trichomonas vaginalis*. Two cases (Cases 19 and 14) were positive

*Preparations supplied through the courtesy of John Wyeth & Brother, Incorporated, Philadelphia.

for monilia on smear and culture, although the vagina was dry and a severe dermatitis was present on the inner aspect of the thighs. No trichomonas or discharge was present. In one case (Case 4) a positive smear and culture were obtained. There were no trichomonads present, but there were a vaginal discharge and a slight dermatitis. In Case 22 smear and culture were both positive although the vagina was dry and crusted, and no trichomonads, discharge, or dermatitis was recorded. Case 23, a girl aged 15 years, presented the most marked symptoms and was treated for a longer period of time than any of the others. This case gave a positive smear and culture for monilia and trichomonas in the presence of a profuse discharge and a severe dermatitis. Case 26 yielded a negative smear and positive culture for monilia in the presence of a discharge and slight dermatitis, although no trichomonads were demonstrable. Case 2 showed a positive smear and culture for monilia. Trichomonads and a severe discharge were present, but there was no dermatitis apparent.

Two patients (Cases 8 and 17) were cured of their infection after receiving one treatment. Fourteen patients (Cases 1, 2, 5, 6, 7, 11, 12, 13, 16, 20, 21, 24, 26, and 28) responded to two treatments each and remained free from symptoms for the three months following treatment during which they were observed. Five patients (Cases 3, 10, 15, 19 and 27) responded to three treatments and remained negative by smear and culture for the same period of time; 5 patients (Cases 4, 9, 14, 18, and 25) responded to four treatments. Cases 22 and 23 required five and eight treatments, respectively. All patients were followed for three months after the cessation of treatment and were found to be negative by both smear and culture at the end of that time.

TABLE I

CASE	AGE	MONILIA ALBICANS		TRICHOMONAS VAGINALIS	DISCHARGE	DRY	DERMATITIS	NUMBER OF TREATMENTS
		SMEAR	CULTURE					
1	29	+	+	-	+	-	-	2
2	32	+	+	+	+	-	-	2
3	38	+	+	-	+	-	-	3
4	22	+	+	-	+	-	+	4
5	23	+	+	-	+	-	-	2
6	28	+	+	-	+	-	-	2
7	52	+	+	-	+	-	-	2
8	21	+	+	-	+	-	-	1
9	31	+	+	-	-	+	+	4
10	56	+	+	-	+	-	-	3
11	18	+	+	-	+	-	-	2
12	28	?	+	-	+	-	-	2
13	40	+	+	-	+	-	-	2
14	23	+	+	-	-	+	+	4
15	36	+	+	-	+	-	-	3
16	27	+	+	-	+	-	-	2
17	31	+	+	-	+	-	-	1
18	33	?	+	+	+	-	-	4
19	25	+	+	-	+	-	+	3
20	19	+	+	-	+	-	-	2
21	25	+	+	-	+	-	-	2
22	41	+	+	-	-	+	-	5
23	15	+	+	+	+	-	+	8
24	24	+	+	-	+	-	-	2
25	16	+	+	-	+	-	-	4
26	48	-	+	-	+	-	+	2
27	25	+	+	-	+	-	-	3
28	36	+	+	-	+	-	-	2

DISCUSSION

Several workers claim that about 20 per cent of the patients harboring *Monilia albicans* do not present clinical symptoms, although they

also claim that the same 20 per cent should be treated.[4] *Monilia albicans* may be found associated with *Neisseria gonorrheae* in rare instances, but more commonly associated with *Trichomonas vaginalis.* Therefore, the growth of *Monilia albicans,* favored by an acid media, is enhanced in the normal vagina, containing a preponderance of Döderlein's bacilli and maintaining a pH of from 4.0 to 4.6.

CONCLUSIONS

1. A satisfactory method for diagnosis both microscopic and cultural is presented, together with the clinical appearance of moniliasis of the vaginal tract.

2. Silver picrate is shown to be a satisfactory form of treatment for vaginal moniliasis.

The authors wish to express their appreciation to Dr. D. H. Wenrich, Professor of Zoology at the University of Pennsylvania, and to Dr. J. H. Clark, Director of the Pathological Laboratories, Philadelphia General Hospital.

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AN UNUSUAL IRREGULARITY OF THE FETAL HEART DURING PREGNANCY

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MARKED irregularities of the fetal heart are usually associated with some condition detrimental to the life or health of the fetus. Bradycardia or premature contractions with a murmur have made possible the diagnosis of congenital heart disease before birth.[1] Marked arrhythmias suggestive of auricular fibrillation have been noticed in association with abortion or premature labor.[2] Holterman[3, 4] has noted premature contractions as an early sign of threatened fetal death in protracted gestation and reports a case in which the baby died before a cesarean section could be performed, along with two other cases in which healthy babies were obtained by cesarean section. Premature contractions during pregnancy have been considered to be due to hydramnion.[5]

The following case is an exception to the general rule, a marked arrhythmia of the fetal heart being present without any apparent abnormality of the fetus.

Mrs. J. K., aged 33, white housewife, one pregnancy six years previously, the history of which showed nothing unusual. Her past and family histories were essentially negative.

When first seen when about five months pregnant, examination showed a healthy woman with the uterine fundus one fingerbreadth below the umbilicus and a faint but regular fetal heart in the midline, rate 140. Shortly afterward she fell and fractured the left fibula for which she wore a plaster splint for one week. The fetal heart was next examined at about six months and again was 140 and regular. However, at the seventh month a decided irregularity was found and was noted thereafter at each one of the nine subsequent prenatal visits. This irregularity showed many variations but usually resembled premature contractions. Sometimes the regu-

lar rhythm was interrupted by a premature contraction every third or fifth beat. Sometimes the premature contraction occurred every second beat for runs of 10 or 100 or more beats. Occasionally there seemed to be nothing but a jumble of sounds. There were no murmurs heard at any time.

An attempt was made to take an electrocardiogram of the fetal heart with leads from the abdomen but a nearby power transformer upset the electrocardiograph just as preparations were completed, although there had been no interference while the mother's tracing was being taken.

As to what prognosis to give the patient we were in doubt. However we did give her a guardedly good prognosis, likening the case to the idiopathic premature contractions of adult life.

The condition continued throughout an uneventful nine hour labor and for six days thereafter. An electrocardiogram taken on the first day after birth proved the nature of the arrhythmia and showed the premature contractions to be ventricular in origin. Repeated examinations after the sixth day and in the next year of life revealed a regular rhythm at all times.

Two hours after delivery the nurse was disturbed by an irregularity of the mother's pulse and then for the first time the mother's heart beat showed premature contractions. These also proved to be ventricular. They continued all during her twelve day stay in the hospital and for at least three and one-half months postpartum, disappearing during exercise only to appear again when the heart slowed down. The patient drank only one cup of coffee and smoked only four or five cigarettes a day. Quinidine sulphate and phenobarbital were given without benefit. As there were no symptoms the medications were discontinued and in the course of another four months the arrhythmia stopped.

This condition is probably not as rare as it would seem, for Hyman[2] in 1930 reported six cases of fetal premature contractions which were demonstrated by use of the phonocardiograph, an instrument which records the fetal heart sounds. In each of these cases healthy babies were born and the arrhythmia disappeared within a few days after birth, the longest lasting about eight days. Somewhat similar cases have also been reported by Lork[6] and by Rihl and Weinzier.[7]

The continuous auscultation of the fetal heart by means of an amplifying stethoscope as recently described by Matthews,[8] and increasing use of fetal electrocardiography will no doubt add much to the study of fetal arrhythmias.

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Kreis, J.: Treatment of a Primary Ulcer of the Vagina After the Menopause With Folliculin, Bull. Soc. d'obst. et de gynéc. **27**: 334, 1938.

The author found in a 64-year-old woman a bloody vaginal discharge coming from an ulcerated area. Biopsy revealed a total absence of epithelium. For six months he cauterized the ulcer but failed to cure it. Then he gave a few injections of estrin and prescribed some by mouth. Bleeding ceased and the ulcer disappeared. Two years have elapsed and there has been no return of the ulcer. Most likely the estrin produced epithelization of the ulcerated area.

J. P. Greenhill.

DICEPHALOUS MONSTER

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(From the Department of Obstetrics, University of Arkansas School of Medicine)

Although this type of monster is not rare, it is uncommon enough to deserve reporting, mainly because it was delivered spontaneously.

The patient was delivered in one of the outlying towns of Little Rock and was sent in to the medical school. A midwife was the only one in attendance and she

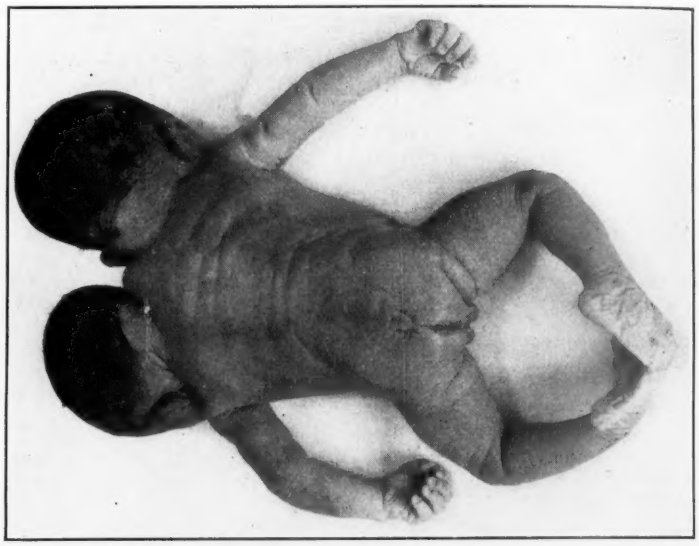

Fig. 1.—Posterior view of the monster.

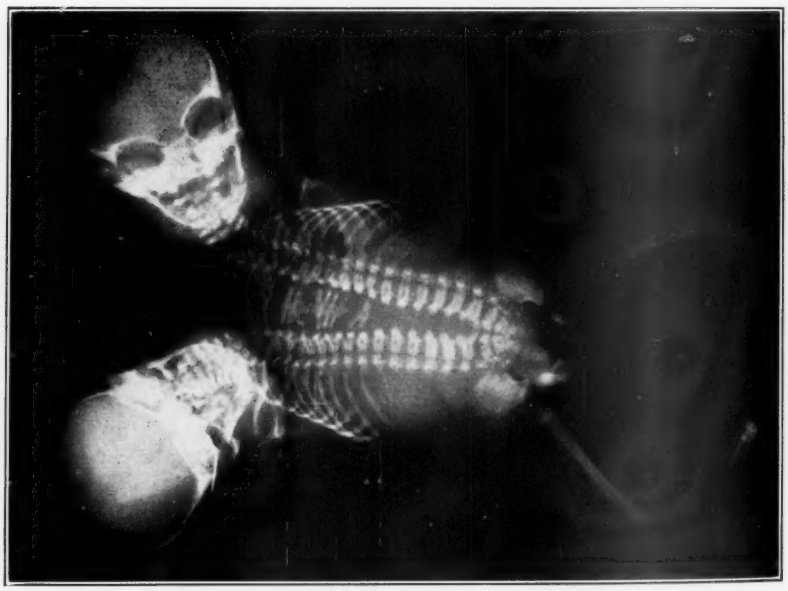

Fig. 2.—X-ray picture showing skeleton formation of the specimen.

stated that the heads presented and that they both delivered at the same time without aid. She also stated that it was born dead. The monster weighed 3,300 gm.

The mother was a colored woman, gravida iv, para iii; the other three children were normal. Duration of labor was fourteen hours. The perineum was inspected by a physician several hours after delivery of the monster, and he found a first degree laceration from a previous delivery with only a slight tear of the mucous membrane from the birth of the monster.

A ONE-HANDED CLOVE HITCH FOR OBSTETRIC MANEUVERS

LE MON CLARK, M.D., CHICAGO, ILL.

IN THE case of a footling presentation or where, for any reason, it is desirable to put a fillet of gauze around the foot or hand of a fetus during the process of labor or delivery, the knot of choice is the clove hitch. With such a knot the fillet may be adjusted to just the right snugness so that circulation will not be cut off and yet tight enough so that it will not pull off. Such a knot will not slip, and thereafter no amount of traction will cause the loop around the presenting part to become any tighter.

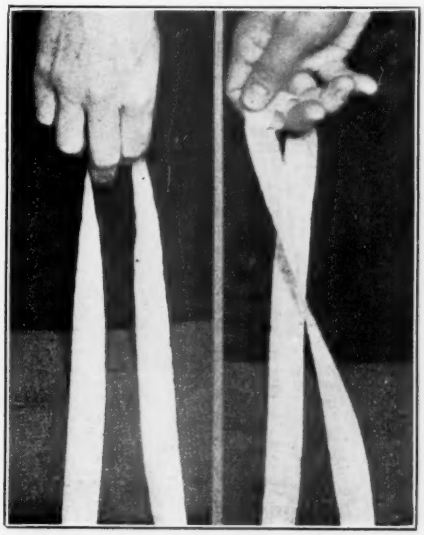

Fig. 1. Fig. 2.

This, of course, is not true of the ordinary slip knot which is so commonly used because it is easy to make and may be made with one hand. Such a knot may slip so that it tightens around the part, causing trouble by impeding the circulation.

There is a method of tying a one-handed clove hitch that is extremely simple. The story of how it was learned is an amusing one. While visiting in Ireland last summer, a group who had had dinner together were staging a round of parlor tricks. When the subject of rope and string tricks came up, a British Army Major contributed the one-handed clove hitch. He, of course, had no appreciation of its value to an obstetrician. But for situations mentioned above, it is most useful.

While the left hand holds the part over which the fillet is to be placed, take a piece of gauze about three feet in length and, holding it around the index and middle

fingers well up towards the palm of the right hand, throw it across the left arm as shown in Fig. 1 with the right hand palm down.

Now turn the right hand over, palm up, so that the two strands of gauze are crossed as shown in Fig. 2.

Next, while preserving the twist in the loop of gauze, move the right hand towards the left arm and place the thumb distal to the distal leg of the original loop, with the fingers around which the loop of gauze is held placed medial to the distal leg of the loop (Fig. 3). Now simply bring the fingers and thumb together around this strand of gauze and pick it up, turning the right hand palm up (Fig. 4).

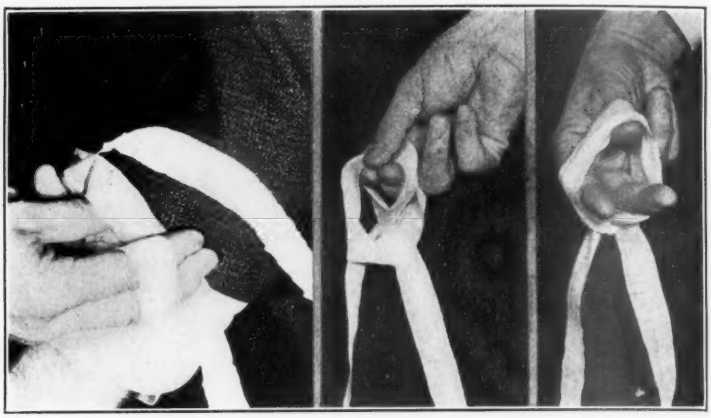

Fig. 3. Fig. 4. Fig. 5.

The two fingers of the right hand now have a clove hitch tied around them. It is a very easy matter to flex the thumb and pass it through this loop (Fig. 5) and reach out with the right hand and take hold of the part around which the clove hitch is to be placed. Then with the left hand, which has thus been released, the knot may be slipped over the presenting part, adjusted as to snugness, and traction applied.

610 West Randolph Street

NEW TYPES OF CERVICAL APPLICATORS FOR TUBAL INSUFFLATION AND UTEROSALPINGOGRAPHY

Emmett D. Colvin, M.D., Atlanta, Ga.

(From the Department of Obstetrics and Gynecology of the Emory University School of Medicine)

TO THE gynecologist and obstetrician, tubal insufflation and uterosalpingography occupy a prominent place in his armamentarium of diagnostic and therapeutic procedures. These two procedures enable him to determine the patency of the oviducts, visualize the uterine cavity, the site of tubal obstruction and serve in the differentiation of uterine from extrauterine masses. Both are indispensable in the diagnosis and treatment of human sterility.

When performing these procedures, in order to avoid false impressions, leakage at the cervix must not occur. To overcome leakage, using ordinary instruments, it is necessary to make counter traction on the cervix by means of a volsellum forceps. This is painful to the patient and traumatizing to the cervix. Another means of avoiding leakage is by pressing the cannula more firmly inward against the cervix during the test. When a short stemmed cannula is used this is objectionable as it

is a frequent source of error. Upward pressure on the cervix causes increased obstructing angulation in the uterocervical canal as the result of counter traction on the uterus by the round ligaments. Also, if upward pressure is too strong during uterosalpingography it will cause peculiar x-ray shadows of the uterine cavity.

With these difficulties in mind the author devised and has extensively used the instruments pictured in Fig. 1. They are made of stainless steel. They have clinically proved most satisfactory, having replaced instruments previously used in his office. Insertion into the cervix is practically painless.

The stems are provided for the attachment of either a Luer syringe or rubber tubing. Thus they can be used for air insufflation or for the injection of opaque media into the uterus and tubes during uterosalpingography.

A common stem with three graduating interchangeable tips is provided (Fig. 1). These have proved to be much more satisfactory than the olive tipped cannula.

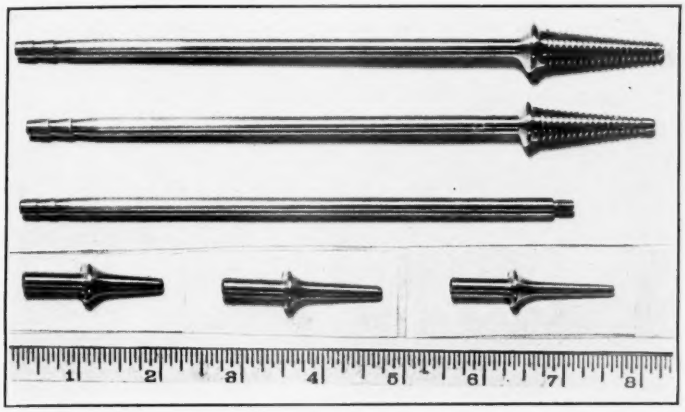

Fig. 1.

Above, two screw tipped stems are seen. These are made in two sizes, large and medium. These two instruments fulfill all requirements. They insure against leakage, cause very little pain during gradual insertion and do not damage the canal. The heads are not detachable from the stems. The screw tip is inserted by gradual rotation in a clockwise direction until slight resistance is felt. Rarely is it necessary to advance the tip to the level of the internal os. With the instrument screwed into the canal, if desired, it is possible to pull the cervix downward during insufflation or injection.

During salpingostomy operations, with the stem screwed into the cervix, the operator can under manometric control inflate the tubes by means of a sterile bulb from the operative field. Thus the actual point of obstruction can be detected after opening the abdomen.

NOTE: These instruments are made by T. L. Keith of Atlanta, Ga.

1259 CLIFTON ROAD, N.E.

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Selected Abstracts

Endocrinology

Dodds, E. C.: The Sex Glands. Their Anatomy, Physiology, and Biochemistry, Brit. M. J. 2: 163, 1937.

A brief discussion of the sex hormone products available in the commercial market is presented. Two sets of hormone substances are connected with the physiology of the sex glands. First, there are those of the anterior lobe of the pituitary gland which activate the secondary sex glands; and second, those secreted by the sex glands after activation.

The hormones of the anterior lobe of the pituitary to date are not available for clinical trial. Experimental work on animals indicates that such extracts of the gland are capable of producing ovulation and corpora lutea in the female, and descent of testis and spermatogenesis in the male.

In the pregnancy urine of certain species the luteinizing fraction of the gonadotropic substance of the anterior pituitary, prolan B, occurs. The blood serum of the pregnant mare during certain stages of gestation contains a very active ovary-stimulating factor. This is available for clinical trial in a stable and standardized form.

The hormones of the ovary are estrone, estradiol, and progesterone. Estrone and estradiol differ one from the other in relative potency only. Estradiol is the more potent of the two. They are available clinically in the form of benzoates. With the administration of estrone or estradiol followed by corpus luteum hormone (progesterone) the menstrual cycle may be reproduced in ovariectomized females. Relatively high dosage of the hormones is required.

The male sex hormone, testosterone, is briefly discussed.

The substances are best absorbed in the body when administered in oily solutions.

F. L. ADAIR AND S. A. PEARL.

Dawson, J. B.: Endocrinology in Obstetrics and Gynaecology, New Zealand M. J. 36: 9, 1937.

The author presents a concise summary of the present status of the estrogenic hormones and their application in clinical fields. He deals with the use of hormones in habitual abortion, hyperemesis gravidarum, toxemia of late pregnancy, and induction of labor.

Sex hormones are discussed in connection with treatment of amenorrhea, oligomenorrhea, functional uterine bleeding at puberty and at the menopause, dysmenorrhea, the menopause, pruritus vulvae and leucoplakia vulvae, gonococcal vaginitis, especially in children; and other rare conditions.

In the use of endocrine therapy, as in every other department of medicine, every case must have individual study and evaluation of dosage.

F. L. ADAIR AND S. A. PEARL.

Boycott, M., and Rowlands, I. W.: The Biological Nature and Quantitative Variation of the Gonadotropic Activity of Pregnant Women's Serum, Brit. M. J. 1: 1097, 1938.

It is shown, in contrast to pregnant mare serum extract, that extracts of human pregnancy serum behave similarly to extracts of urine of pregnancy, in that, (1) they cause only a limited response in the rat ovary, judged by increase in ovarian weight, and (2) they produce no follicular growth in the ovary of the hypophysectomized rat.

The concentration of gonadotropic substance in human serum rises rapidly from the sixth week, is at a maximum from the eighth to the twelfth weeks, and thereafter declines to a low level, which is fairly constant from the twentieth week to the end of pregnancy.

No gonadotropic substance was detected in serum of nonpregnant women.

The significance of the presence of gonadotropic substance in relation to the luteal activity of the placenta is discussed.

F. L. Adair and S. A. Pearl.

Bowes, Kenneth: Treatment of Menstrual Irregularities by a New Sex Hormone Preparation, Brit. M. J. 2: 904, 1937.

The author reports a small series of cases in which the hormone obtained from pregnant mare serum (the follicle-stimulating hormone of the hypophysis) was used successfully in the treatment of menstrual disorders. The product used was "antostab."

Results of the therapy were studied by clinical means and by the strip-cutting curette of uterine biopsy for microscopic changes. While the series is too small for definite conclusions, the results are gratifying and justify mention.

F. L. Adair and S. A. Pearl.

Davidson, Stephen M.: Oestrin and Progestin in Secondary Amenorrhoea, Brit. M. J. 2: 1190, 1936.

The author describes 4 patients in whom the administration of large doses of estrin produced menstruation, following a secondary amenorrhea in 2; one incompletely established menses, and one failure. Owing to the expense, the treatment is applicable only to a few select patients. These experiments further elucidate the action of the ovarian secretions upon the endometrium and the role they play in the menstrual cycle.

The estrin is responsible for the growth and development of the uterus. It is of value clinically in sexually immature and underdeveloped individuals. Progestin has been established as the factor required to produce the glandular changes in the endometrium which must take place before the endometrium can harbor and embed a fertilized ovum. It must, therefore, be a part of the therapeutic regime in amenorrhea and sterility. Only a small dose of progestin is required in clinical use—5 units; whereas, estrin must be given in huge doses, i.e., up to one million I.U. to establish a cycle. Different workers vary in the dosage advised.

F. L. Adair and S. A. Pearl.

Koch, W.: Hormonal Influence of Sex in the Dog, Klin. Wchnschr. 15: 1135, 1936.

The author describes a series of experiments in which he attempted to influence the sex of subsequent litters in a large series of dogs. These animals were fed large quantities of the follicle hormone and the percentage of males in the subsequent litters was compared with the percentage of males in previous litters. These previous litters showed 84.7 males to every 100 females. Following the administration of the hormone the ratio changed to 126.5 males for every 100 females, an increase of over 50 per cent. It would seem, therefore, to be possible to influence or change the sex of subsequent offspring by hormonal administrations.

Ralph A. Reis.

Foss, George L.: Temporary Postponement of Menstruation by Oestradiol Benzoate, Brit. M. J. 2: 10, 1937.

There are occasions when temporary postponement of menstruation is greatly desirable and justifiable. The author favors such therapy once or twice only during an individual's lifetime.

He obtained good results by the use of 50,000 I.B.U. of estradiol benzoate (six times as physiologically active as estrone). The standardized preparation used in this work was progynon B oleosum. The injections are best given at close intervals on alternate days, especially towards the expected time of onset, and even after ovulation takes place good results are possible with large doses.

Such a temporary inhibition of the anterior pituitary by estrin does not seem deleterious, according to the author's experience. Injections must be made intramuscularly, especially in obese patients, to avoid leakage from the tissues. The essence of this therapy is to maintain a high superthreshold level of estradiol benzoate until after the time when menstruation is expected.

F. L. Adair and S. A. Pearl.

Westman, A.: The Effect of the Gonadotropic Anterior Pituitary Hormone Antex on the Ovaries of Women, Acta obst. et gynec. Scandinav. 17: 492, 1937.

Westman administered Antex which is a gonadotropic anterior pituitary hormone to women who were to be operated upon. He then removed the ovaries and studied them. In seven women he found an increased follicle growth in the ovaries after the injection of the gonadotropic hormone. Of 7 women who had myomas, 5 showed excessive follicle formation in the ovary after the injections. Hence the effect of gonadotropic hormone on the human ovary is the same as it is on the ape ovary. This effect was produced in normally functioning ovaries. The author is now trying to find out if the same effects can be produced in cases of primary and secondary amenorrhea.

J. P. Greenhill.

Hamblen, E. C., and Ross, R. A.: Responses of the Human Ovary to Gonadotropic Principles, Endocrinology 21: 726, 1937.

An analysis of observations upon 85 patients after gonadotropic therapy and of detailed reports of the ovarian responses of 7 patients is made. Six of the 7 cases reported in detail were patients in whom presumptive diagnoses of anovulatory failure had been made. The total doses in these patients ranged from 6,000 to 24,250 R.U., the daily doses varying from 400 to 8,000 R.U. The observed ovarian responses, judged either by direct inspection of ovaries, by their microscopic study, or by inferential studies of the endometrium, do not warrant an assumption that ovulation and corpus luteum formation had resulted from such therapy.

J. Thornwell Witherspoon.

Moricard, F., and Saulnier, F.: Follicular Development in the Ovary of Women Stimulated by Injections of Mitosine (Gonadotropic Hormone From the Serum of Pregnant Mares), Bull. Soc. d'obst. et de gynéc. 27: 132, 1938.

In 1937 Moricard and Saulnier published a paper reporting that they had been able to stimulate follicular development in women by means of gonadotropic hormone of serum from pregnant mares. In the present paper the authors give the details of their work on more than 2,000 animals. They observed: (1) In gravid mares there is a hormone in the serum which is capable of stimulating massive follicle development in immature mice. (2) When this substance is injected in doses of 1/1,000 mg., it can cause a tenfold increase in the weight of the uterus of immature mice. (3) The response of the ovary to the action of mare's serum is variable.

The authors give case reports of four women treated with serum from pregnant mares to prove that this serum can produce follicle development.

J. P. Greenhill.

Costa, P., and Cantilo, E.: Inhibition of Friedman Test by Large Doses of Theelin, Compt. rend. Soc. franç. de gynec. 8: 19, 1938.

The authors report a case in which they caused a positive Friedman test to become negative by giving large doses of theelin. The test became again positive as soon as the theelin injections were stopped. Therefore it is proved that the secretion of the gonadotropic hormone of the anterior pituitary can be inhibited by large doses of theelin.

In spite of the huge doses of estrin administered, an abortion did not take place. This the authors attribute to the use of large amounts of corpus luteum after the theelin was given. These authors found that abortion frequently followed the administration of large amounts of theelin when corpus luteum was not subsequently used.

J. P. GREENHILL.

Neuman, Hans Otto: Adrenal Cortex and Sexuality, Arch. f. Gynäk. **160:** 481, 1936.

Adrenal cortex deficiency produces a hypofunction of sex function which leads to atrophy of the glands and to amenorrhea. The author describes a patient with Addison's disease in whom he found a menopausal type of atrophy of the uterine mucosa. Hormonal therapy resulted in a restoration of functioning endometrium and a return of normal menstrual flows.

Hyperfunction of the adrenal cortex produces precocious puberty in children, virilismus and interrenalism in the sexually mature woman, but practically no changes in sex characteristics after the menopause. The author describes three cases of hypernephroid blastomas. One of these patients had undergone marked masculinizing changes which disappeared after removal of the tumor. She subsequently became pregnant and had a normal full-term child.

The author also describes three hypernephroid blastomas of the ovaries. He discusses the causes of this typical masculinizing effect of hypernephroid blastomas and concludes that their effect is produced indirectly by way of the hypophysis.

RALPH A. REIS.

Moricard, R.: Trophic Disturbances in the Genitalia Secondary to Hypophysectomy in a Woman, Bull. Soc. d'obst. et de gynéc. **25:** 777, 1936.

The author reports the case of a woman who had a hypophysectomy done because of a tumor. There had never been any functional disturbances in the genitalia, but following the operation there resulted an atrophy of the entire genital tract.

J. P. GREENHILL.

Krane, W.: Investigations in the Effects of Hysterectomy on the Endocrine Functions of the Ovary and the Pituitary in the Mature Woman, Arch. f. Gynäk. **164:** 101, 1937.

The author describes a new and much shorter method for the quantitative determinations of estrogen content and contrasts it with the previous standard method, i.e., benzol extraction. He then reports his findings in patients in whom hysterectomy was performed during the reproductive years. There is no increase in prolan production which is evidence that ovarian atrophy does not set in after hysterectomy. The production of estrogen continues at its normal level for years following hysterectomy. The latter does not, therefore, induce any castration effect. Studies carried out over a 54 day cycle in a patient who had undergone hysterectomy six years previously showed the normal and usual variations in the estrogen level. The cyclic curves of increased and decreased production of estrogen followed the normal curves and the author concludes that ovulation continues normally after hysterectomy.

RALPH A. REIS.

Heiberg, B.: The Excretion of Gonadotropic Hormone in the Urine of Women After Ovarian Autotransplantation, Acta obst. et gynec. Scandinav. **17:** 440, 1937.

In agreement with others, B. Heiberg found that when the amount of gonadotropic hormone in the urine is increased beyond fairly low values, it is as a rule a sign of decreased ovarian function. He examined the urine of five women in whom autotransplantation had been performed. He found that for several weeks after operation there was no increase in the excretion of gonadotropic hormone. Then during the next few months there was an increased amount of this hormone corresponding to a diminished function of the implanted tissue because of insufficient adhesions. Then for many months there was a diminution in the amount of the gonadotropic hormone which proved that the transplant was functioning as normal ovarian tissue. Finally in all five patients, increased amounts of the hormone appeared in the urine indicating decreased activity of the transplants. Apparently the climacteric was setting in. The clinical symptoms which these patients exhibited corresponded with the hormone studies.

J. P. GREENHILL.

Kosakae, J., Okamoto, S., and Kosuge, T.: Are the Sexual Hormones Excreted Through the Sweat Glands? Jap. J. Obst. & Gynec. **20:** 279, 1937.

It has been demonstrated that the sex hormones and the hormones of the anterior pituitary gland are absorbed through the skin. It has also been shown that there is a connection between absorption through the skin and the presence of sweat glands. The authors attempted to find out whether the sex hormones were eliminated through the sweat glands because they looked upon these glands as avenues of excretion just as the urine is. In order to collect large quantities of sweat they placed their patients in heat chambers. The authors examined the sweat of three women over a period of many weeks but failed to find a trace of the female sex hormones. They likewise analyzed the sweat of five men for anterior pituitary hormones but could not detect any of these hormones.

J. P. GREENHILL.

Venning, Eleanor Hill, and Browne, J. S. L.: The Urinary Excretion of Sodium Pregnandiol Glucuronidate in the Human Menstrual Cycle, Endocrinology **21:** 720, 1937.

The quantitative excretion of sodium pregnandiol glucuronidate in the human menstrual cycle in 10 cases is reported. This compound is considered to be an excretion product of progesterone. It is only excreted in the luteal phase of the menstrual cycle and appears in the urine within twenty-four to forty-eight hours after ovulation. The excretion of this compound is continuous for a certain period, varying from three to twelve days in the cases studied; in 6 of the 10 cases the period was ten to twelve days. Bleeding occurs from one to three days following its disappearance from the urine. The total amount of pregnandiol excreted per period varied from 3 to 54 mg. The measurement of this compound in the menstrual cycle offers a means of determining the duration and functional activity of the corpus luteum.

J. THORNWELL WITHERSPOON.

Englehart, E., and Riml, O.: The Metabolic Function of the Corpus Luteum, Arch. f. Gynäk. **164:** 36, 1937.

It had been previously reported by the authors that corpus luteum extracts produce changes in metabolism and they had, therefore, concluded that the corpus luteum has a direct effect upon metabolism. Further studies led them to report that the changes in metabolism previously reported were due to some as yet un-

defined chemical in the lipoid extract and not to the corpus luteum hormone. They report further that the corpus luteum has no effect upon thyroid function but does effect glycogen storage in the liver, by producing an increase.

RALPH A. REIS.

Macht, David I.: Methods of Demonstrating the Activity of Corpus Luteum, Surg. Gynec. Obst. **66**: 733, 1938.

A résumé of all kinds of experimental data found in scientific literature regarding the physiologic function of the corpus luteum is presented.

Three lines of investigation by the writer and his collaborators with water-soluble corpus luteum preparations are described.

A study of vaginal smears revealed that injections of corpus luteum extracts distinctly inhibited the estrus cycle of guinea pigs.

Injection of corpus luteum extracts in mice inhibited a tendency to hypertrophy of the uterus induced by injections of estrogenic follicular extracts.

Corpus luteum extracts elicited characteristic responses from uterine muscle of guinea pigs and cats, Fallopian tubes of pigs, and vasa deferentia of white rats.

In the three classes of experiments the same extracts induced parallel and comparable results, thus demonstrating that the activity of corpus luteum preparations may be shown by several convenient methods.

WILLIAM C. HENSKE.

Haffner, J.: The Progestin Content of Mature and Immature Human Placentas, Acta obst. et gynec. Scandinav. **18**: 25, 1938.

The author made quantitative determinations of progestin in full-term placentas and found that there was on an average a one-half Clauberg rabbit unit present in each placenta. In placentas obtained from pregnancies in the first three months, he found an average progestin content in each placenta of between one-third and one-half Clauberg rabbit unit. The author, therefore, maintains that progestin is formed in the placenta in the early months and he believes that habitual abortions are due to failure on the part of the placenta to produce progestin.

J. P. GREENHILL.

Jeanneny, G., Hirtz, G., and Merveille, P.: Reflections on the Uterine Hormone Functions, Rev. franç. de gynéc. et d'obst. **32**: 149, 1937.

The authors raise the question as to whether or not the uterus possesses an internal secretion. They cite the following as evidence in support of an affirmative answer: The occurrence of metrorrhagia, and even amenorrhea in the presence of fibroids is an evidence of uterine dysfunction. The partial or total conservation of the uterus during gynecologic operations reduces postoperative complications and assures continued function of the ovaries, left behind or grafted. Removal of a uterus results in degeneration of ovaries left in situ.

The authors are convinced of a utero-ovarian functional synergy and they lay down the following rules: Conserve the ovaries and uterus totally or in part as often as possible. In cases of bilateral oophorectomy with conservation of the uterus, always graft an ovary. After hysterectomy with conservation of the ovaries, make a uterine graft. After removal of the uterus and adnexa make a graft of both uterus and ovary. The authors have prepared a uterine extract which they have administered by mouth as well as subcutaneously for dysmenorrhea with good results.

J. P. GREENHILL.

Byrom, F. B.: The Effect of Oestrogenic and Other Sex Hormones on the Response of the Rat to Vasopressin, Lancet **1**: 129, 1938.

A group of immature unspayed rats was injected with gonadotropic and a second group with estrogenic hormone following which 50 international units of vasopressin per 100 gm. body weight were injected. Examination of the kidneys in these animals

revealed greater damage than in controls not receiving the sensitizing injections. The effect of the gonadotropic hormone was absent in spayed animals. Progesterone did not prevent the sensitizing effect of estrin, and testosterone propionate seemed to augment the effect.

The author states that the sensitivity of the rat to toxic doses of vasopressin can be greatly enhanced by preliminary treatment with estrogenic hormone. It is recalled that the injection of vasopressin causes eclampsia-like lesions in animals, that the eclamptic patient is said to be hypersensitive to vasopressin and that the period of pregnancy in which eclampsia is peculiar is characterized by a high output of estrogenic hormone. It is suggested that estrin-sensitization may be in some way concerned with the genesis of eclampsia.

CARL P. HUBER.

Gonnet, Bansillon, and Bucher: New Observations on the Use of Estrogenic Substance for Inducing Labor, Bull. Soc. d'obst. et de gynéc. **26**: 514, 1937.

The authors report eight instances in which they induced labor by means of estrogenic substance. In one case a single injection resulted in the expulsion of a fetus which had been dead for some time. The other seven inductions were in women with contracted pelves. There was only one failure. To obtain successful results with estrogenic substance it is necessary to purge the patient and then give quinine and pituitary extract. The authors believe there are no dangers associated with this procedure.

J. P. GREENHILL.

Cotte, G., Mileff, A., and Meyer, C.: The Action of Folliculin on the Vaginal Mucosa of Women, Rev. franç. de. gynéc. et d'obst. **32**: 683, 1937.

The authors have shown that in women administration of estrogenic substance alone suffices to produce mucification of the vaginal epithelium and the reappearance of glycogen in it. In some of the authors' patients the ovaries were absent, hence the effect on the vaginal mucosa was due entirely to the injected estrin. These results agree with those obtained by Papanicolaou and by Klaften whose work was unfamiliar to the present authors until they had completed their studies. The effects produced on the vaginal epithelium by estrin may be used not only to select proper cases for estrin therapy but also to judge the effectiveness of this kind of treatment.

J. P. GREENHILL.

Wilde, H., and Wolf, B.: The Hormone Treatment of Gonorrheal Vulvovaginitis in Children, Med. Klin. **33**: 122, 1937.

The authors treated seven children who had gonorrheal infections with estrogenic hormone. Five children had an infection of the vagina and urethra, one had the infection in the vagina, urethra, and rectum and the seventh had an isolated vaginal gonorrheal infection. All of these children were given 10,000 unit doses of estrogenic hormone in addition to local treatment. The results were not favorable. Furthermore complications were observed. All the children had swelling of the breasts, which subsided after the hormone treatment was stopped. Two children (aged 9 and 11) began to masturbate vigorously. In both children the labia and clitoris were markedly swollen. The authors' experience led them to believe that hormone therapy in young girls results in long-standing disturbances in the glands of internal secretion, because in their cases physical and psychic changes persisted for many weeks. Only the future can tell whether disturbances will manifest themselves during the reproductive years.

J. P. GREENHILL.

Cesa, I.: Influence of Hormonal Action on the Cervical Glands, Compt. rend. de la Soc. franç. de Gynéc. **6**: 266, 1936.

In animals there exists a great variation in the condition of the cervix. This region is always badly differentiated in immature animals and among castrated

animals. It attains its full development only under the influence of estrogenic substance hence only at estrus. It is at this time that the special characteristics of the cervical glands are most marked. The action of the corpus luteum hormone on the glands consists of stimulation of their secretion. These facts explain the development of the cervix and its glands in women and also the variation found in the cervix at different parts of the menstrual cycle.

Small doses of estrogenic substance stimulate the cervix. Since large doses produce intense changes in the epithelium of the cervix of animals, the author cautions against the prolonged administration of large doses of these substances alone. Corpus luteum hormone produces resolution of these changes hence the danger consists in giving estrogenic substance alone. It is probable that estrogenic substance and the corpus luteum hormones are not the only hormones produced by the ovary, nevertheless, they are antagonistic substances.

J. P. GREENHILL.

Zuckerman, S.: Effects of Prolonged Oestrin-Stimulation on the Cervix Uteri, Lancet **1**: 435, 1937.

Carcinogenic power has been ascribed to estrogenic substances, largely because of results occurring in "cancer strains" of mice. Such effects have not been induced in the reproductive organs of women and monkeys by excessive or prolonged dosage with estrogenic substance.

Prolonged and massive dosage of this material results in the development of cystic endometrial hyperplasia. By withdrawing the estrogenic stimulus the changes are reversed.

A review of the report of Overholzer and Allen is given. The author was unable to show any cancerous or precancerous lesions of the cervix in monkeys receiving much larger amounts of estrogenic substances. A metaplasia was noted at the junction of the squamous and columnar epithelium. This metaplasia is orderly, and the basement membranes remain intact.

It is concluded that there is little need in clinical practice for prescribing the hormone over a prolonged period; and the effect of estrin can be reversed by its withdrawal. It is suggested that the best way to administer estrogenic hormone clinically is in courses of two to four weeks with intervals for the "estrin-withdrawal."

H. CLOSE HESSELTINE.

Ziskin, Daniel E.: Effect of Hormonal Treatment on Gums and Oral Mucosa of Women, J. Dent. Research **16**: 367, 1937.

The hormones progynon B and follutein injected respectively into women in the treatment of amenorrhea and prolonged menstruation bleeding, affect the gingivae and oral mucosa. Progynon B causes hyperkeratinization and hyperplasia of the oral epithelium. The gums of women receiving progynon are uniformly in a healthier state than those receiving follutein. The gums of women receiving the latter hormone show evidence of inflammation and degeneration both grossly and microscopically, probably as result of a direct effect of follutein.

These findings made on six women resemble closely previously reported observations of the author made on female rhesus monkeys.

HUGO EHRENFEST.

Moricard, R., and Cauchoix, J.: Macroscopic Fibroids Obtained Experimentally in the Rabbit by the Continuous and Prolonged Action of Dihydrofolliculin Benzoate, Bull. de la Soc. d'obst. et de gynéc. **27**: 272, 1938.

As indicated by the title the authors were able to produce macroscopic fibroids in female rabbits by continuous injections of the benzoate of folliculin. The doses given were small but the injections were administered over a period of four and one-half to seven months.

J. P. GREENHILL.

Loeser, A. A.: Resorption and Action of Follicular Hormone Rubbed Into the Skin, J. Obst. & Gynaec. Brit. Emp. **44**: 710, 1937.

His experiments showed that the skin of monkeys (baboons) is penetrable by follicular hormone. Estrus can be produced in castrated monkeys by rubbing the hormone into the skin. In women from whom the ovaries have been removed or in women suffering from ovarian insufficiency, clinical symptoms can be produced by rubbing the hormone into the skin; this indicates that the skin absorbs and is penetrated by the follicular hormone. The skin of women with normally functioning ovaries is penetrable by the follicular hormone to an individually varying degree. There appears to be a connection between ovarian insufficiency and changes in the skin (atrophy). Administration of follicular hormone is of value in skin affections.

J. P. GREENHILL.

Ito, Hajazu and Kon: Percutaneous Action of the Sex Hormones, Zentralbl. f. Gynäk. **61**: 1094, 1937.

These writers found that folliculin is absorbed through the skin by female monkeys and rats, so that in them estrus, uterine hypertrophy, and mammary development can be produced. The effect depends somewhat on the vehicle used for the hormone. The most marked effect is obtained from a solution containing 60 per cent of alcohol, while water, skin cream, lanolin and vaseline cause a decrease in strength. The percutaneous method of administration is preferable to the oral when a prolonged effect is desired. The male sex hormones can be equally well administered through the skin.

J. P. GREENHILL.

Migliavacca, A.: Contribution to the Local Therapy of Pruritus Vulvae, Atti. Soc. ital. di ostet. e ginec. **34**: 178, 1938.

The author experimented with the action of follicular hormone applied directly to the external genitalia as a salve (lanolin and vaseline used as the vehicle).

The results were somewhat favorable. The accurate selection of cases appeared indispensable for a successful therapeutic result. Pruritus vulvae associated with ovarian dysfunction and with atrophic changes accompanying the menopause is the type of pruritus lending itself most favorably to this form of local treatment.

The author claims as advantages of local treatment that the therapeutic action is more prompt and direct, and requires a smaller quantity of the hormone, hence is more economical.

A. A. MARCHETTI.

Wetterwald, M.: The Hormonal Treatment of Pruritus Vulvae in the Menopause, Rev. franç. de gynéc. et d'obst. **32**: 572, 1937.

Wetterwald is convinced that large doses of estrogenic substance will surely and rapidly cure pruritus vulvae during the menopause. He gives an injection of 10,000 international benzoate units (50,000 ordinary international units) every second day. It is important to continue these injections for a while after the pruritus has ceased. In a few cases serious uterine bleeding has been reported but the author has never encountered such a case. This bleeding is to be expected because large amounts of estrogenic substance can produce hyperplasia of the endometrium.

J. P. GREENHILL.

Correspondence

To the Editor:

I have read with great interest the editorial entitled "The Dosage of the Estrogens," which appeared in the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY 36: September, 1938. The confusion that arises, as you point out, from the various trade names of these estrogenic compounds has become extensive, and the addition of another international unit for standardization of these preparations has not helped this situation. In order to assist, if possible, in the clarification of this situation, may I refer to the following points in the above-mentioned editorial?

In the first and third paragraphs, theelol is indicated to be synonymous with estradiol, whereas in fact, it actually is a different compound. Theelol is estriol and constitutes a third type of estrogenic preparation with characteristic physiological properties differing from estrone or estradiol.

In the definition of the international unit in the third paragraph there is undoubtedly a misprint, that is, "0.1 gamma (1/10,000 of a gram)" should read 0.1 gamma (1/10,000,000 of a gram) or (1/10,000 of a milligram). A more important consideration than the definition of the international unit is the fact *that two international units of estrogenic materials have been established,* one for estrone, the other for estradiol. Both units have the same mass (0.1 gamma) but refer to different chemical entities. The quantitatively different physiological potency of these compounds is not apparent when expressed in international units. For example, 1000 I.U. of estrone (theelin) are not equivalent to 1,000 I.U. of estradiol (progynon).

The separation of the various commercial products you have mentioned into the proper class of estrogens may be of interest.

Amniotin and theelin: estrone or ketohydroxyestrin

Theelol and emmenin: estriol

Progynon B and DH, and menformon: estradiol.

Sistomensin, while carrying some estrogenic activity, from a clinical point of view can hardly be regarded as a satisfactory source of this material (Wiesbader and Kurzrok, Endocrinology **23**: 32, 1938).

I am forwarding this information to you not as a criticism of your editorial but as an addition to it, in the hope that it will aid in the resolution of the confusion you have pointed out.

Jack M. Curtis,
Associated Pharmacologist, United States
Department of Agriculture.

Washington, D. C.
Nov. 12, 1938

NOTE: It would be desirable if international authorities were able to enforce the use of the simple chemical names of estrone, estradiol, and estriol and urge that these be substituted for the generally employed trade names. Clarification undoubtedly would follow this procedure and further confusion be avoided.

Editor.

Books Received

THE TECHNIQUE OF CONTRACEPTION. An Outline. By Eric M. Matsner, M.D. Foreword by Frederick C. Holden, M.D. Fourth edition, illustrated, 50 pages. The Williams & Wilkins Company, Baltimore, 1938.

DER ZYKLUS DER FRAU. Reform des Ehelebens. Von Dr. Jules Samuels, Chirurg-Frauenarzt. Mit 43 Abbildungen im Texte, 175 Seiten. Verlag G. Naeff, Haag, Holland, 1938.

THE VITAMINS AND THEIR CLINICAL APPLICATIONS. A Brief Manual. By Professor Dr. W. Stepp, director of I. med. Klinik, University of Munich, Dozent Dr. Kuehnau, in Wiesbaden, and Dr. H. Schroeder, Associate, I. med. Klinik, Munich. Translated by Dr. Herman A. H. Bouman, Minneapolis, Minn. The Vitamin Products Company, Milwaukee, Wis., 1938.

CANCER, With Special Reference to Cancer of the Breast. By R. J. Behan, M.D., F.A.C.S., Cofounder and formerly director of the Cancer Department of the Pittsburgh Skin and Cancer Foundation. Illustrated, 844 pages. C. V. Mosby Company, St. Louis, 1938.

THE ROCKEFELLER FOUNDATION. Annual Report, 1937. New York, 1938.

THE PRINCIPLES AND PRACTICE OF OBSTETRICS. By Joseph B. DeLee, professor of obstetrics and gynecology, emeritus, University of Chicago, etc. Seventh edition, entirely reset. 1211 pages with 1277 illustrations on 985 figures, 271 of them in color. W. B. Saunders Company, Philadelphia, 1938.

STOECKEL'S HANDBUCH DER GYNAEKOLOGIE. Dritte, voellig neubearbeitete und erweiterte Auflage. Zehnter Band. Gynaekologischer Beitrag zur Urologie von Dr. W. Stoeckel, Universitaet Berlin; I. Teil, 738 Seiten mit 432 Abbildungen; II. Teil, 438 Seiten mit 261 Abbildungen; III. Teil, 1008 Seiten mit 468 Abbildungen. Verlag von J. F. Bergmann, Muenchen, 1938.

THE NEW-BORN INFANT. A Manual of Obstetrical Pediatrics. By Emerson L. Stone, M.D., associate clinical professor of obstetrics and gynecology, School of Medicine, Yale University, etc. Second edition, thoroughly revised, 291 pages, not illustrated. Lea & Febiger, Philadelphia, 1938.

TEXTBOOK OF ANATOMY AND PHYSIOLOGY. By Diana Clifford Kimber, Carolyn E. Gray, A.M., R.N., and Caroline E. Stackpole, A.M., associate in biology, Teachers College, Columbia University. Tenth edition, revised and rewritten. 276 illustrations, 643 pages. The Macmillan Company, New York, 1938.

SEASON OF BIRTH. Its Relation to Human Abilities. By Ellsworth Huntington, Yale University. 473 pages with 104 figures. John Wiley & Sons, Inc., New York, 1938.

LIFE AND LETTERS OF FIELDING H. GARRISON. By Solomon R. Kagan, M.D. With an Introduction by Professor James J. Walsh. 287 pages, The Medico-Historical Press, Boston, 1938.

Items

American Board of Obstetrics and Gynecology

The general oral, clinical and pathological examinations for all candidates, Part II Examinations (Groups A and B), will be conducted by the entire Board, meeting in St. Louis, Missouri, on May 15 and 16, 1939, immediately prior to the annual meeting of the American Medical Association. Notice of time and place of these examinations will be forwarded to all candidates well in advance of the examination dates.

Candidates for reexamination must request such reexamination by writing the Secretary's Office before the following date: Part II, April 1, 1939. Candidates who are required to take reexaminations must do so before the expiration of three years from the date of their first examination.

Application for admission to Group A, May, 1939, examinations must be on file in the Secretary's Office by March 15, 1939.

Application blanks and booklets of information may be obtained from Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

The Central Association of Obstetricians and Gynecologists

The Tenth Annual Meeting of this association was held at the Hotel Radisson in Minneapolis, October 6 to 8, 1938. The following officers were elected for the coming year:

President, Ralph A. Reis, Chicago
President-Elect, Jennings C. Litzenberg, Minneapolis
Vice-President, Thomas B. Sellers, New Orleans University Hospital
Secretary-Treasurer, William F. Mengert, Iowa City
Assistant Secretary, Harry J. Davis, Topeka

Dr. William T. Black, a member of the Advisory Editorial Board of the JOURNAL, died at Memphis, Tenn., on December 8, 1938. An extended obituary will be published in a forthcoming issue.

Errata

In the article by Caldwell, Moloy, and D'Esopo "Studies on Pelvic Arrests" in the December issue, page 935, line 27 the word "inefficient" should read "in efficient."

In the legend for Fig. 4, page 937, the description of numbers *3, 4, 5* should read "*3*, medium in the anterior pelvis (in front); *4*, medium in the posterior pelvis (behind); *5*, Low-medium in the posterior pelvis (behind)."

On page 938, line 5, the reference to the numbers in Fig. 4 should read "(Fig. 4*A, 5, 4*)."

On page 944, the table should be "Table VIII" instead of Table III.

American Congress on Obstetrics and Gynecology

Cleveland, Ohio, September 11 to 15, 1939
Preliminary Program

Five-day sessions are planned, mornings from 9 A.M. to 11 A.M., with special programs devoted to professional groups; noon, from 11:45 A.M. to 1:15 P.M., round table discussions; afternoons, 2:30 P.M. to 4:30 P.M., joint sessions of general interest to all members attending the Congress; evenings, Monday through Thursday, 8:30 P.M., speakers of national prominence—open to all members and the public.

In the Medical Section, the following topics will be considered—further details will appear in later issues as these become available:

Monday, September 11, 1939

The Thyroid and Pregnancy; Heart Disease and Pregnancy; Diabetes and Pregnancy; Tuberculosis and Pregnancy; Nutritional Factors and Pregnancy; The Surgical Abdomen Complicated by Pregnancy; The Treatment of Abortions.

Tuesday, September 12, 1939

The New Conception of Ovarian Neoplasms; Carcinoma of the Uterus; Endometriosis; Ectopic Pregnancy; Sterility in the Female.

Wednesday, September 13, 1939

Reduction of the Operative Incidence in Obstetrics; Labor Complicated by the Contracted Pelvis; Dystocia Due to Soft Parts; Pathology and Treatment of the Third Stage of Labor.

Thursday, September 14, 1939

Present-Day Fundamental Knowledge of Hormones and Endocrine Glands; Problems of Adolescence; Problems of Menopause; Diseases of the Mammary Gland.

Friday, September 15, 1939

Sulfanilamide in Obstetrics and Gynecology; Pyelitis; Chronic Pelvic Infections; Immediate and Remote Complications Following Labor.

Round Tables

Running concurrently each day 11:45 A.M. to 1:15 P.M.

The Toxemias of Pregnancy; Genital Infections; Obstetric and Gynecologic Hemorrhages; the Fetus and the Newborn; Forceps, Occipito-Posterior, and Breech Presentation; Anesthesia, Analgesia and Amnesia in Labor.

Joint Afternoon Sessions

Monday, September 11, 1939, Neonatal Care.
Tuesday, September 12, 1939, Plans for Prevention and Control of Uterine Cancer.
Wednesday, September 13, 1939, Extension Education on Maternal and Neonatal Care.
Thursday, September 14, 1939, Economic Aspects of Maternal Care.
Friday, September 15, 1939, Correlation of and Attempt to Digest All Proceedings.

Joint Evening Sessions

Monday, September 11, 1939, Legal Aspects of Maternity.
Tuesday, September 12, 1939, Humanitarian Aspects.
Wednesday, September 13, 1939, Sociologic Aspects.
Thursday, September 14, 1939, Ethical Aspects.

Membership

Membership fee is $5, which includes a year's membership in The American Committee on Maternal Welfare and registration in The American Congress on Obstetrics and Gynecology, Cleveland, Ohio, September 11 to 15, 1939. Application for membership in The American Congress on Obstetrics and Gynecology may be made to Headquarters Office: The Annex, 650 Rush Street, Chicago.

WILLIAM T. BLACK
1875—1938

UNIV. OF MICH.